Chemoenzymatic Synthesis of ent-Neopinone

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Abstract

The present thesis describes the chemoenzymatic synthesis of *ent*-neopinone. The total synthesis of neopinone was accomplished in 14 steps from β-bromoethylbenzene. The synthesis began with a microbial oxidation of bromobenzene by *Escherichia coli* JM109(pDTG601) and features a Heck reaction, aldol condensation and a 1,6-conjugate addition.

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List of Abbreviations

2,4 DNP	2,4-dinitrophenyl hydrazine
Ac	acetyl
ADDP	1,1'-(azodicarbonyl)dipiperidine
AIBN	azobisisobuytronitrile
Boc	*tert*-butyloxycarbonyl
$(Boc)_2O$	di-*tert*-butyl dicarbonate
Bn	benzyl
Bz	benzoyl
CSA	camphorsulfonic acid
cAMP	cyclic adenosine monophosphate
dba	dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]udec-7-ene
DEAD	diethyl axodicarboxylate
DIAD	diisopropyl axodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DMAP	dimethylamino pyridine
DME	dimethoxyethane
DMF	N,N-dimethylformamide
DMP	2,2-dimethoxypropane
DMSO	dimethyl sulfoxide
DPPE	1,2-*bis*-(diphenylphosphino)ethane

DPPF	1,1'-*bis*-(diphenylphosphino)ferrocene
DPPP	1,3-Bis(diphenylphosphino)propane
NEt_3	triethylamine
FAB	fast atom bombardment
IBX	2-iodoxybenzoic acid
i-Pr	isopropyl
IPTG	β-isoproplythiogalactopyranoside
IR	infrared spectroscopy
J	NMR coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
LiHMDS	lithium bis(trimethylsilyl)amide
*m*CPBA	*meta*-chloroperoxybenzoic acid
MEM	methoxyethoxymethyl
MOM	methoxymethyl
Mp	melthing point
MS	mass spectroscopy
NADH	Nicotinamide adenine dibucleotide
NBS	N-bromosuccinimide
NMO	N-methylmorpholine-N-oxide
NMR	nuclear magnetic resonance
PAD	potassium azodicarboxylate
PCC	pyridinium chlorochromate
PEG	poly(ethylene glycol)

Ph	phenyl
*p*PTS	pyridinium 4-toluenesulfonate
*p*TsOH	*para*-toluenesulfonic acid
Py	pyridine
SMEAH	Sodium bis(2-methoxyethoxy)aluminumhydride
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TDO	toluene dioxygenase
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	tetramethylsilane
Ts	tosyl

1. Introduction

An ideal synthetic target is one that incorporates structural complexity and utility. Such molecules provide chemists with interesting synthetic problems to tackle and allow for the development of new methods. Opium alkaloids fulfill these criteria as they have been used extensively in medicine for the treatment of pain. Despite morphine's small size, its complexity stems from the completely dissonant connectivity.[1] Opiate alkaloids are harvested from opium poppy species grown in Iran, Afghanistan, Turkey and India. Because of the political unrest in these countries and the world wide demand of opiates, a short and efficient synthesis of morphine and its congeners is required.

The Hudlicky group has a long history of exploring the development of a practical synthesis of morphine alkaloids. The current thesis will focus on a chemoenzymatic approach to *ent*-neopinone. Our current strategy relies on the construction of the C ring of neopinone from 3,5-cyclohexadiene-1,2-diol **6**. This chiral building block is obtained from the biooxidation of β-bromoethylbenzene using *Escherichia coli* JM109(pDTG601). We envision the conversion of diol **6** to the homoallylic ethylamine derivative **5**, which will allow for the coupling of the A and C rings yielding a suitable precursor for the closure of the D ring intermediate via subsequent aldol condensation and 1,6-conjugate addition that should conclude the synthesis of neopinone (Figure 1). This thesis provides an historical overview of arene microbial oxidations and the use of these biooxidations in selected syntheses, as well as a historical overview of opium alkaloids and selected syntheses. The

detailed description of our approach to ent-neopeinoine **1** comprises the discussion section of the dissertation.

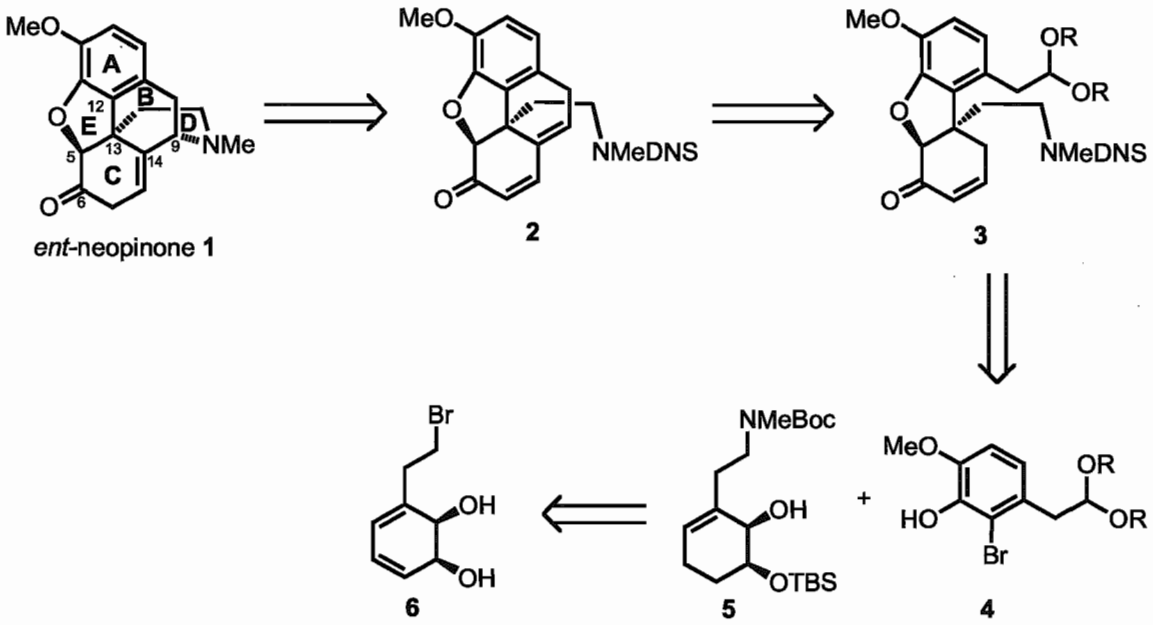


Figure 1. Retrosynthetic analysis for ent-neopinone. Morphine numbering and lettering shown.

2. Histrorical

2.1 Microbial Oxidation of Arenes

2.1.1 History of aromatic dioxygenases

In early twentieth century, Störmer was the first to report the metabolism of aromatic substrates when he observed the bacterium *Bacillus hexcarbavorum* could use benzene and toluene for growth.[2] Over half a century later it was shown that the products of this metabolism were catechols.[3] In 1968, David Gibson published his seminal work on a bacteria (*Psqudomonas putida*) that utilized solely toluene or benzene as its carbon source.[4-5] He showed that benzene and toluene were consumed at equal rates to that of oxygen consumption during metabolism. This suggested that the metabolic pathway did not proceed through the formation of an epoxide during the metabolism of arenes. To further investigate the possible mechanism, Gibson incubated cell extracts with proposed intermediates. Phenol and *trans*-dihydrobenzenglycol were metabolized slower than catechol and cis-dihydrobenzene glycol. This led Gibson to propose a mechanism for the transformation of benzene to catechol shown in figure 2.

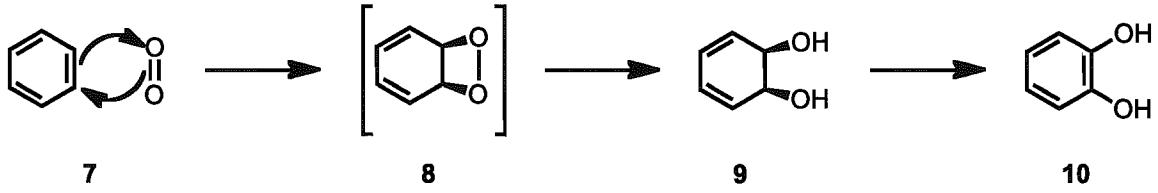
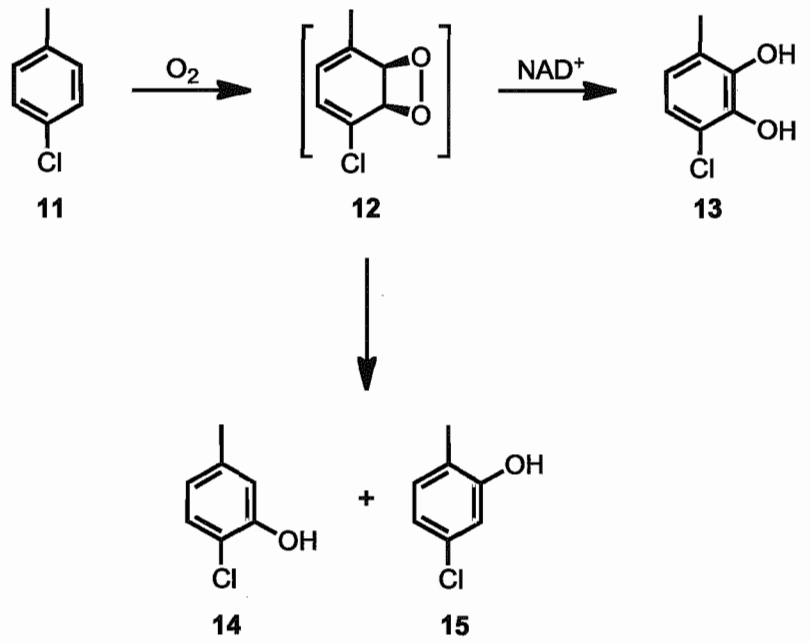


Figure 2. Proposed pathway for catechol formation by *P. putida.*

In order to confirm the proposed metabolic pathway and the evidence of the intermediate **9**, Gibson began working with the bio-oxidation of substituted aromatics. When *P. putida* was incubated with *p*-chlorotoluene **11,** two metabolites were produced, a catechol **13** and an unknown compound **12.**[5] When metabolite **12** was subjected to acidic conditions it quickly decomposed to phenols **14** and **15** (scheme 1). This degradation study as well as spectroscopic studies led to the proposal of (+)-*cis*-4-chloro-2,3-dihydroxy-1-methylcyclohexa-4,6-diene **12.** To confirm the hydroxyl groups of the catechol originated from one molecule of oxygen, $^{18}O_2$ labeled oxygen studies were preformed.[6] This confirmed his proposal for the incorporation of one molecule of oxygen for each molecule of substrate.



Scheme 1. Proposed pathway for the metabolism of *p*-chlorotoluene by toluene-grown cells of *P. putida*

In 1970, a mutant strain of *P. putida* was discovered that did not contain the genes encoding for the enzymes which are required to process the *cis*-cyclohexandienediol.[7] This allowed for the isolation of the diol in sufficient amounts so that stereochemical studies could be performed. Gibson was able to isolate what he believed to be (+)-*cis*-2,3-dihydroxy-1-methyl-4,6-cyclohexadiene **21** produced by the mutant strain (*P. putida* 39/D) when digesting toluene **20**. Evidence at the time indicated that microbial metabolism of arenes proceeded through *trans*-intermediates via hydrolysis of a *cis*-epoxide as shown in figure 3.

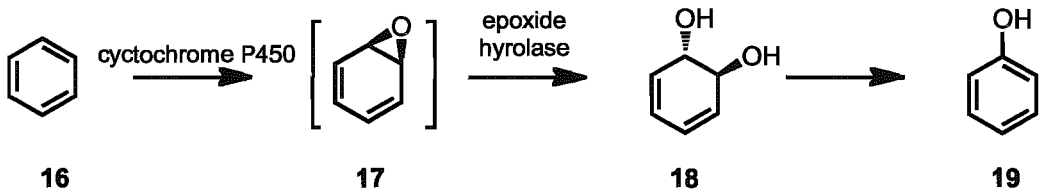
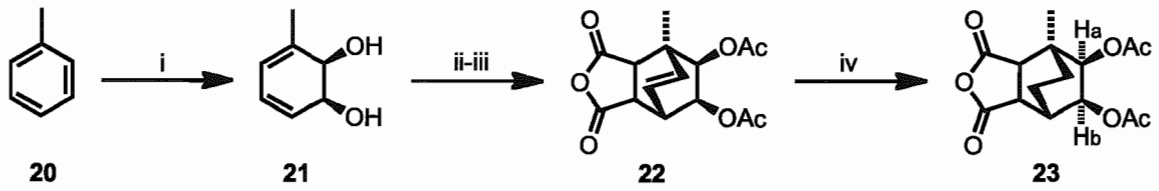


Figure 3. *trans*-Diols resulting for hydrolysis of *cis*-epoxides

To determine the stereochemistry of isolated metabolite **21**, the diol was protected as the diacetate and condensed with maleic anhydride. Hydrogenation of the Diels-Alder adduct **22** produced the fully saturated tricycle **23** which was analyzed by NMR spectroscopy (scheme 2).



Reagents and conditions: i) *P. putida* 39/D; ii) Ac_2O; iii) maleic anhydride; iv) H_2, Pd/C.

Scheme 2. Proof of relative stereochemistry of (+)-*cis*-2,3-dihydroxy-1-methyl-4,6-cyclohexadiene **24**.

Analysis of the spectroscopic data confirmed that the vicinal protons H_a and H_b in compound **23** are in a *cis* configuration to each other. To determine absolute stereochemistry of the *cis*-hexadienediol, Gibson performed a hydrogenation of **21** producing two diastereomers **24** and **25** (figure 3). Seperation of the diastereomers was performed with their monobenzoate derivates via column chromatography and subsequent ester hydrolysis provided the pure samples of the diastereomers **24** and **25**. Jones oxidation of **25** furnished the previously reported (-)-2R-methyladipic acid **26** and comparison of physical properties established the absolute stereochemistry of the *cis*-diol as 1S,2R. [8]

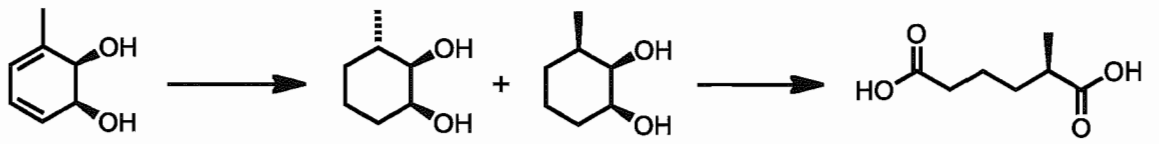


Figure 3. Absolute stereochemical proof of the *P. putida* 39/D metabolite **21**.

However, through this stereochemical proof the stereocenters of the *cis*-diol were destroyed during oxidation. Thus the assignment was inferred from the facial

selectivity of the hydrogenation. It was not until Hudlicky's synthesis of $PGE_{2\alpha}$ in 1988, that the absolute stereochemistry was proved unequivocally.[9]

2.1.2 Isolation and characterization of the toluene dioxygenase

The development of the mutant strain (*P. putida* 39/D) by Gibson allowed for the isolation of the gene coding for the enzyme responsible for the accumulation of the *cis*-cyclohexadienediols. This enzyme was coined toluene dioxygenase (TDO).[10] The nucleotide sequence of genes responsible for the metabolism of arenes was determined by thorough studies of mutant strains of *P. putida*[11] (figure 4). This allowed for the expression of these genes in *E. coli* and helped confirm the metabolic pathway of the wild type strain.

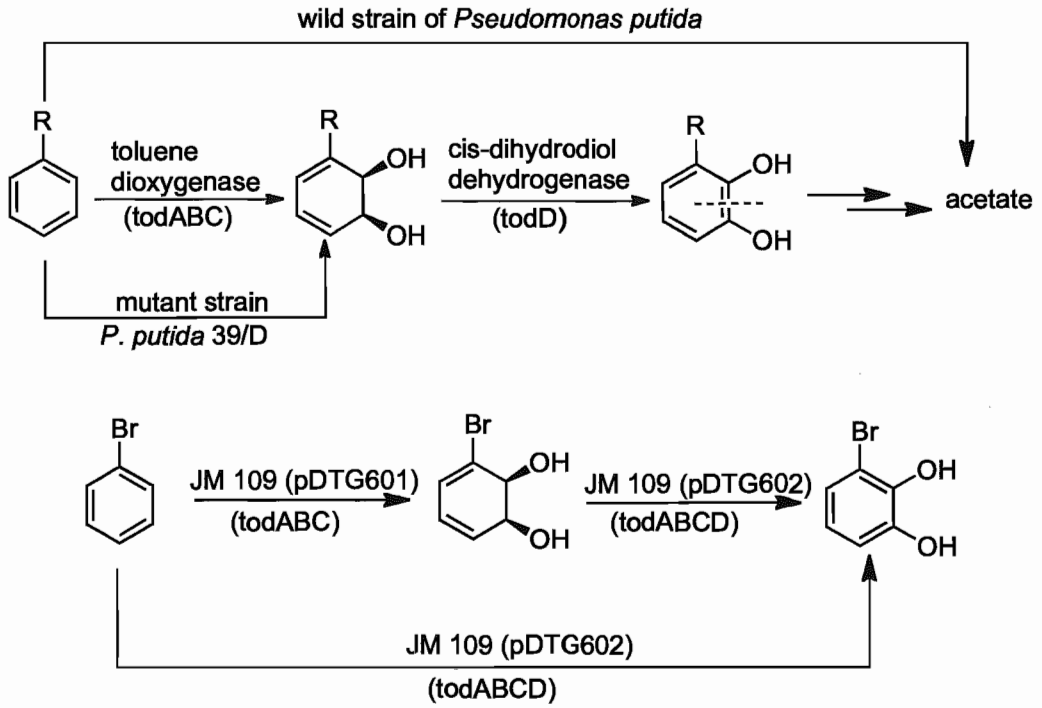


Figure 4. Metabolism of arenes by *P. putida* and recombinant strains of *E. coli*.[12]

The TDO genes were expressed in the recombinant *E. coli* JM109(pDTG601). This allowed for the over-expression of the TDO enzyme and thus the production of *cis*-cyclohexadienediols in sufficient amounts to be used sensibly as synthetic precursors. Other recombinant organisms JM109(pTDG602) and JM109(pDTG603) were created to allow for the production of catechols and 2-hydroxy-6-oxo-2,4-hetpadienoates, respectively.

The expression of the genes *E. coli* now allowed for these recombinant organisms to be used as tools in synthetic organic chemistry.[13-14] The use of these recombinant *E. coli* organisms for biooxidations of arenes provides distinct advantages compared with the use of strains from *P. putida.* *E. coli* has been thoroughly researched and thus its growth conditions have been well optimized. *P. putida* requires the use of arenes as inducers for production of the desired enzymes. However the inducer is also a substrate and thus must be separated from the desired metabolite. In the recombinant *E. coli,* the inducer is a sugar analogue, β-isopropylthiogalactopyranoside (IPTG). Therefore eliminating the complication of having the inducer also be a substrate for the *E. coli.* Also the organism has been engineered with ampicilin resistances so it is robust and the cultures are not easily contaminated with other bacteria. The other advantage of the recombinant *E. coli* is the fact that it contains a plasmid, which has multiple copies of the genes responsible for the toluene dioxygenase allowing for greater expression and higher yields of diols.

2.1.3 Substrate scope and specificity

Since Gibson's isolation of the first *cis*-cyclohexadienediol more than 400 substrates of the toluene dioxygenase have been identified. Some of the best substrates are bromo-, chlorobenzene, styrene, naphthalene, *m*-dibromobenzene and β-bromoethylbenzene. Despite the large number of metabolites only a fraction of these have been used in total synthesis.[12] The dihydroxylations by TDO follow a predictable manner with respect to regio- and stereoselectivity. Boyd's research has allowed for the development of a model to account for the regio and stereoselectivity.[15] The greater difference in relative size between the substituents (S and L) the higher the enantiomeric ratio of diol obtained. This model was later extended as shown in figure 5 to include larger, more conformationally flexible substituents, as well as taking into consideration substituents in the *ortho* and *meta* positions of substituted arenes. [16-17]

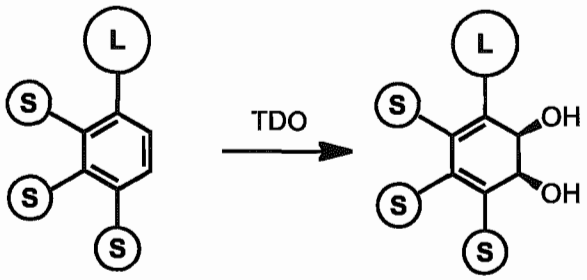


Figure 5. Boyd's expanded model for the prediction of regio- and stereoselectivity of TDO dihydroxylations.

2.1.4 Applications of toluene dioxygenase in synthesis.

In 1983, researchers at Imperial Chemical Industries were the first to exploit the *cis*-cyclohexadienediols in their preparation of polyphenylene **28** via a radical polymerization reaction (Figure **6**).[18]

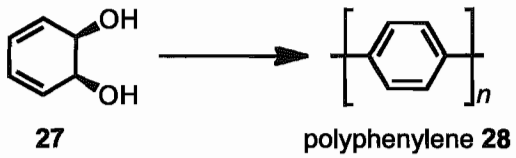
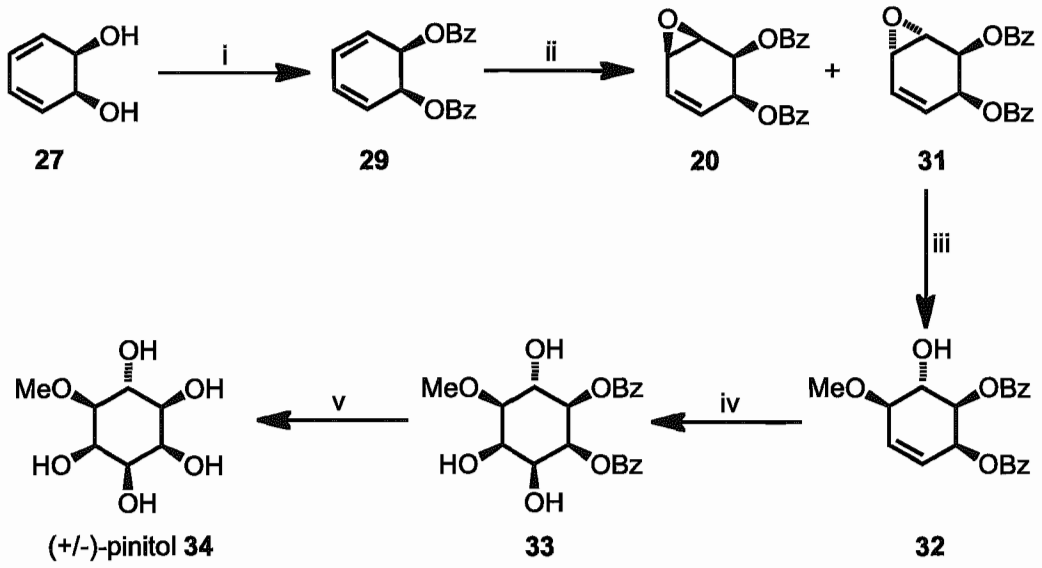


Figure 6. ICI preparation of polyphenylene from *cis*-cycylohexadienediol.

However, in the process of reforming the arene the diol functionality was deystroyed. The first stereochemical exploitation of the *cis*-cyclohexadienediols did not occur until Ley reported the synthesis of (+/-)-pinitol **34** as seen in scheme 3.[19]

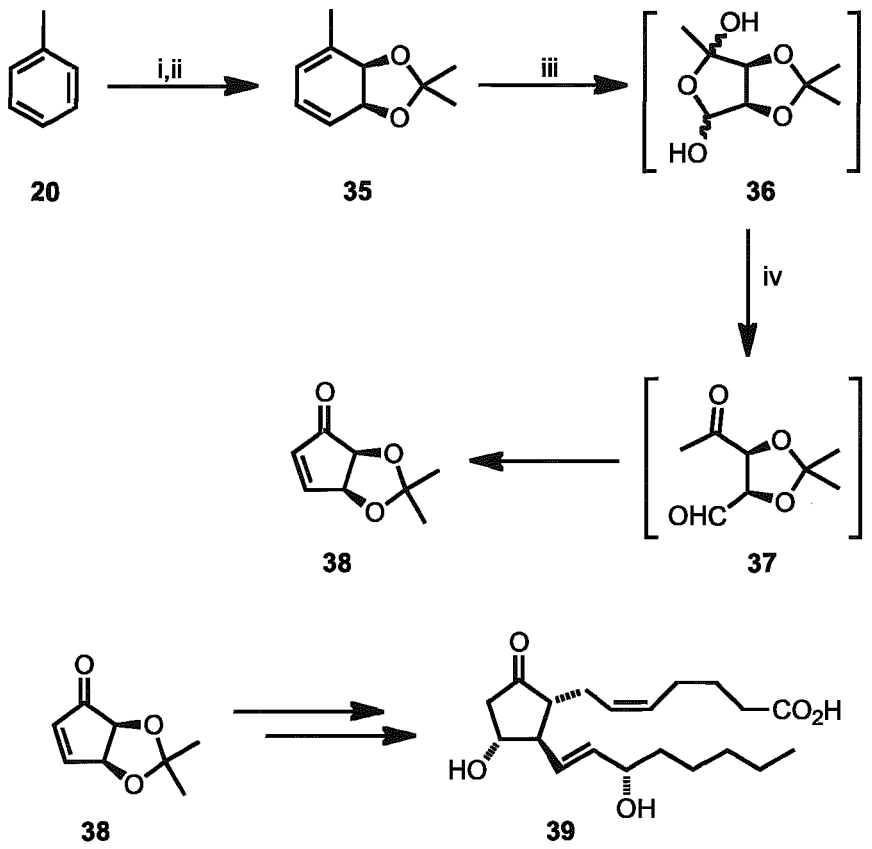


Reagents and conditions: i) PhCOCl, pyridine, DMAP, 0 °C–RT (84%); ii) *m*-CPBA, $ClCH_2CH_2Cl$, pH 8 phosphate buffer (**30** in 14%, **31** in 73%); iii) MeOH, camphorsulfonic acid (88%); iv) OsO_4, NMO, *t*BuOH/THF/H_2O (61%); v) NEt_3, MeOH, H_2O;

Scheme 3. Ley's synthesis of (+/-)-pinitol **34**.

In his synthesis he utilized the benzyl protected diol **29** to allow for facial selective epoxidation of the diene followed by selective opening of the vinyl epoxide with methanol. Installation of the remaining hydroxyls was performed by treatment of **32** with OsO_4 followed by deprotection of the diol to yield (+/-)-pinitol **34** in 35% from benzene. The use of the diols to direct further transformations and the steric and electronic differentiation of the dienes are now standard strategies in the use of *cis*-cyclohexadienediols in synthesis.

The first enantioselective application of *cis*-cyclohexadienediols was performed by Hudlicky in the formal synthesis of $PGE_{2\alpha}$ **39** in 1988.[9] The formal synthesis of prostanoid synthon **38**, which was previously converted to $PGE_{2\alpha}$ by Johnosn,[20] was completed in only four steps; a vast improvement upon previously reported syntesis.[12] As shown in Scheme 4, Transformation of toluene with *Pseudomonas putida* 39/D afforded the corresponding diol in a yield of 3 g/L of culture. Protection of the diol as its acetonide gave compound **35**.

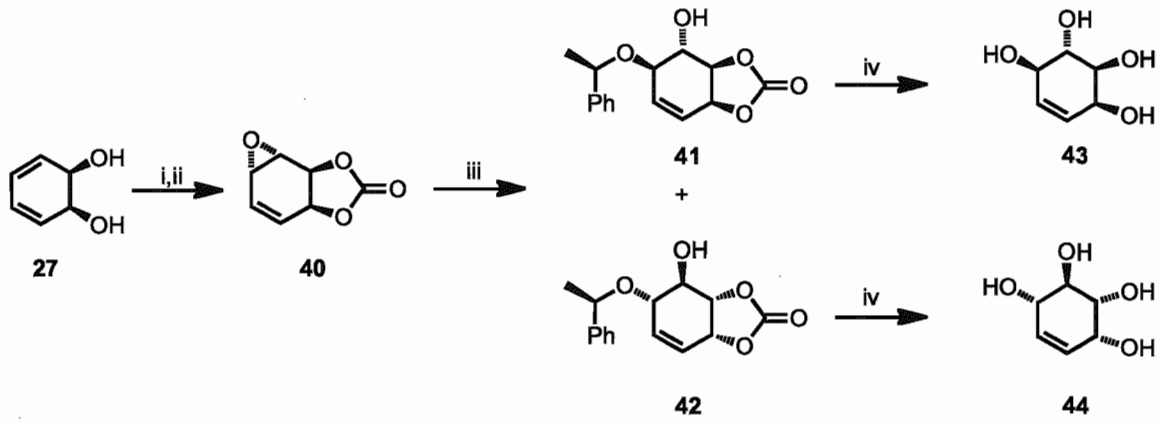


Reagents and conditions: i) *P. putida* 39/D; ii) DMP, *p*TsOH, RT; iii) O_3, Me_2S; iv) Al_2O_3 (neutral), DME, reflux.

Scheme 4. Hudlicky's formal synthesis of $PGE_{2\alpha}$.

Oxidative cleavage of the diene with ozone provided the ketoaldehyde **37** which underwent intramolecular aldol condensation to give the prostanoid synthon **38.** This synthesis demonstrated the incredible value of the diol metabolites as chiral precursors for natural products or other synthetic targets. Research in the application of these metabolites as chrial synthons for synthesis has been lead by Ley, Banwell, Boyd and Hudlicky. The most significant contributions of these researchers will be presented in further detail.

In addition to Ley's synthesis of (+/-)-pinitol **34**, he also developed an enantiodivergent approach to (+)- and (-)-conduritol F **43** and **44**.[21] Starting for the same *cis*-cyclohexa-3,5,-diene-1,2-diol **27** as he used in his synthesis of (+/-)-pinitol **34**, he treated the diol with dimethyl carbonate to form the cyclic carbonate followed by epoxidation with *meta*-chloroperoxybenzoic acid that resulted in a one-pot preparation of epoxide **40** (scheme **5**). At this point, regioselective opening of the epoxide with (*R*)-(+)-*sec*-phenethyl alcohol in the presence of tetrafluoroboric acid-diethyl ether complex gave two diastereomers **41** and **42**.



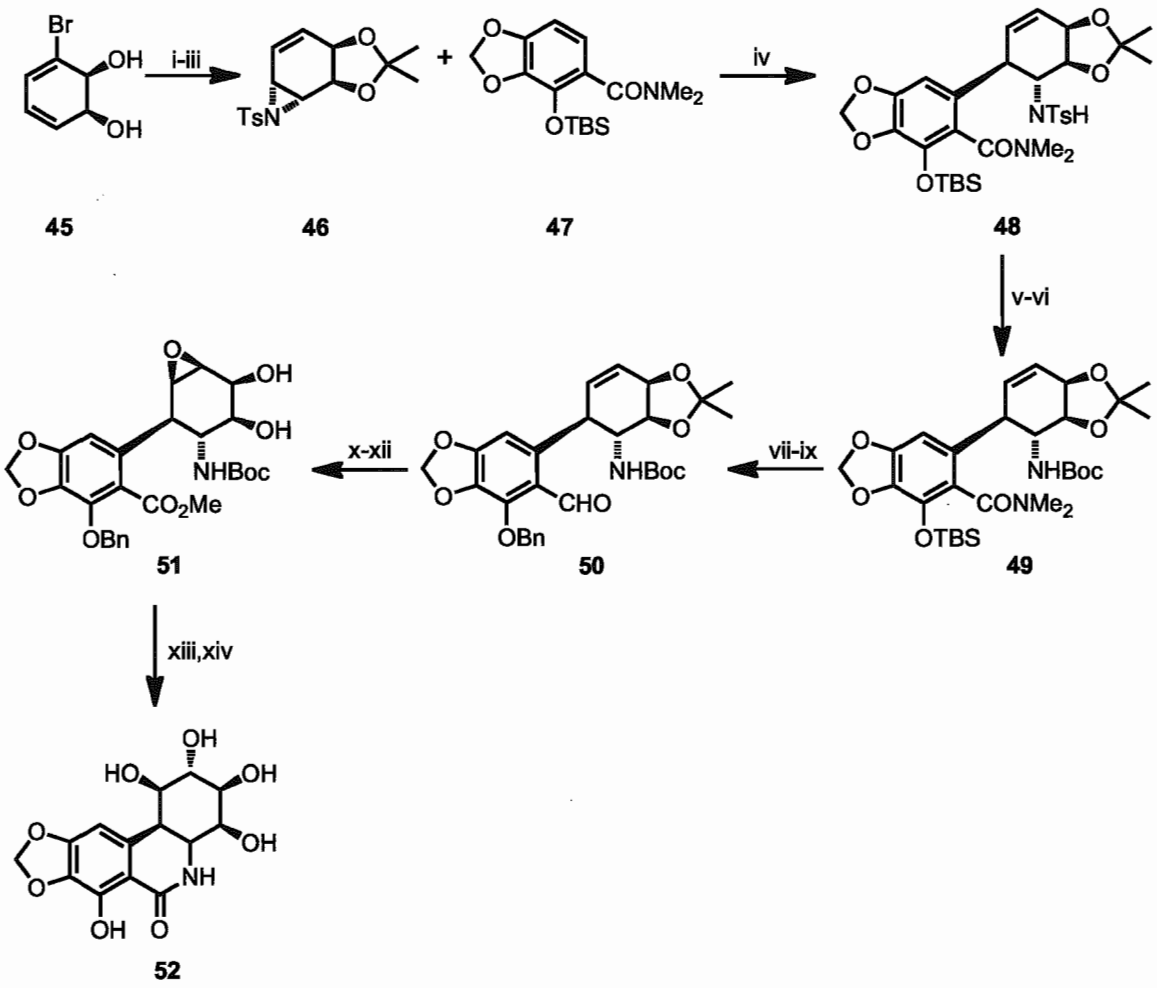
Reagents and conditions: i) $(MeO)_2CO$, MeO^-Na^+, MeOH; ii) *m*CPBA, CH_2Cl_2; iii) (*R*)-(+)-*sec*-phenethyl alcohol, $HBF_4 \bullet OEt_2$, CH_2Cl_2; iv) Na/NH_3, Et_2O, -78 °C.

Scheme 5. Enantiodivergent synthesis of (+)- and (-)-conduritol F.

After their separation the benzyl ethers were reduced under dissolving metal conditions to cleanly cleave the carbonate and the benzyl ether to furnish (+)- and (-)-conduritol F **43** and **44**.

Hudlicky has exploited the *cis*-cyclohexadienediols as a chiral synthon for the synthesis of numerous natural protducts including the synthesis of several of the

Amaryllidaceae alkaloids[22-25] especially the first asymmetric total synthesis of (+)-pacratistatin **52** from (1*S-cis*)-3-bromo-3,5,-cyclohexadiene-1,2-diol **45**.[26]. Acetonide protection of the diol moiety followed by aziridination procedure described by Evans[27] and finally tri-*n*-butyltin hydride reduction of the vinyl bromoide gave the tosyl aziridine **46** (Scheme 8). Amide **47** was subjected to ortho metalation followed by treatment with copper(I) cyanide formed the lithium cyanocuprate species which selectively opened the aziridine **46**.



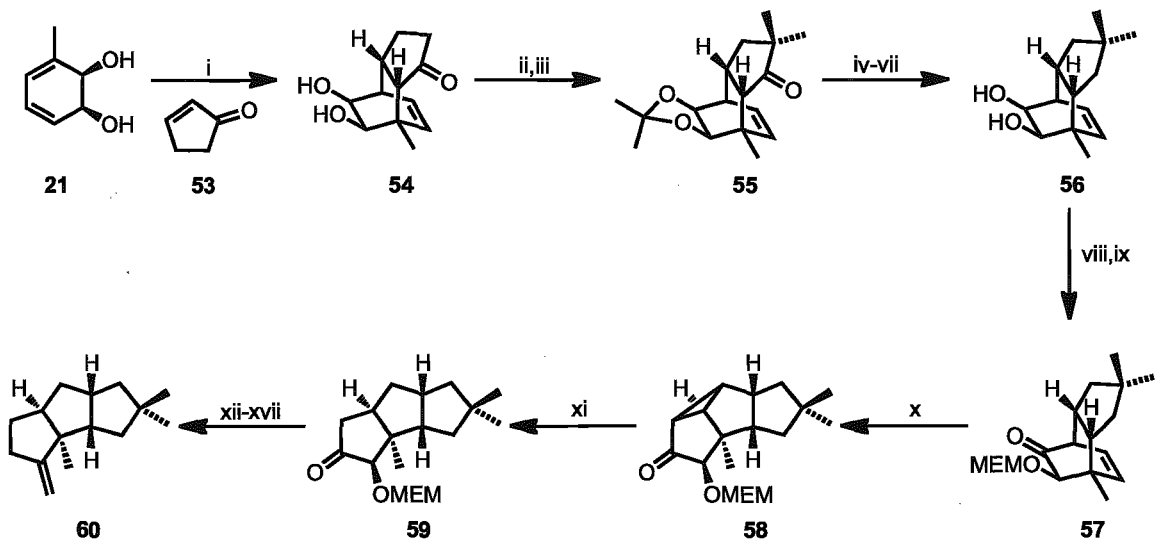
Reagents and conditions: i) DMP, *p*-TsOH, CH_2Cl_2; ii) PHI=NTs, $Cu(acac)_2$, CH_3CN; iii) $n$$Bu_3SnH$, AIBN, THF, PhMe, reflux; iv) a) *s*-BuLi, TMEDA, THF, -90 °C; b) CuCN, -90 °C to -20 °C; c) $BF_3 \cdot OEt_2$, -78 °C – RT; v) a) *s*-BuLi, THF, b) $(Boc)_2O$; vi) Na/antharacene, DME, -78 °C; vii) TBAF, THF 0 °C; viii) SMEAH, THF, morpholine, -45 °C; ix) BnBr, K_2CO_3, DMF; x) a) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O; b) CH_2N_2, Et_2O; xi) AcOH, THF, H_2O, 60 °C; xii) *t*-BuOOH, $VO(acac)_2$, PhH, 60 °C; xiii) H_2O, BzO^-Na^+ (cat.), 100 °C; xiv) $Pd(OH)_2/C$, H_2, EtOAc.

Scheme 8. First enantioselective synthesis of (+)-pancratistatin **52**.

Treating the sulfonamide **48** with *s*-butyl lithium followed by Boc anhydride allowed for the removal of the tosyl group by dissolving metal reduction resulting in the carbamate **49**. The silyl ether was cleaved using tetrabutylammonium fluoride

and the dimethyl amide was then reduced to the aldehyde using sodium bis(methoxyethoxy)aluminium hydride. The phenol was then protected as the benzoyl ether to provided aldehyde **50**. Oxidation of the aldehyde followed by treatment with diazomethane afforded the methyl ester. Hydrolysis of the acetonide and subsequent treatment with $VO(acac)_2$ and di-*tert*-butyl peroxide (directed by the free hydoxyl groups) formed the epoxide **51.** To conclude the synthesis the epoxide was treated with aqueous sodium bicarbonate at 100 °C which stereoselectively opened the epoxide, thermally cleaved the carbamate and cyclized the δ-lactam followed by hydrogenation to remove the benzoyl ether provided (+)-pancratistatin **52.**

Banwell utilized the *cis*-cyclohexadienediol **21** derived from toluene in his synthesis of the sesquiterpenoids (-)-hirsutene **60**[28] and (+)-histuric acid.[29] Banwell's synthesis of (-)-hirsutene **60** started with a high pressure Diels-Alder cycloaddition between cis-cycloxhexadienediol **21** and 2-cyclopenten-1-one **53** to form the *syn*-addition product in 70% yield and *anti*-product in only 9% yield (Scheme 6).



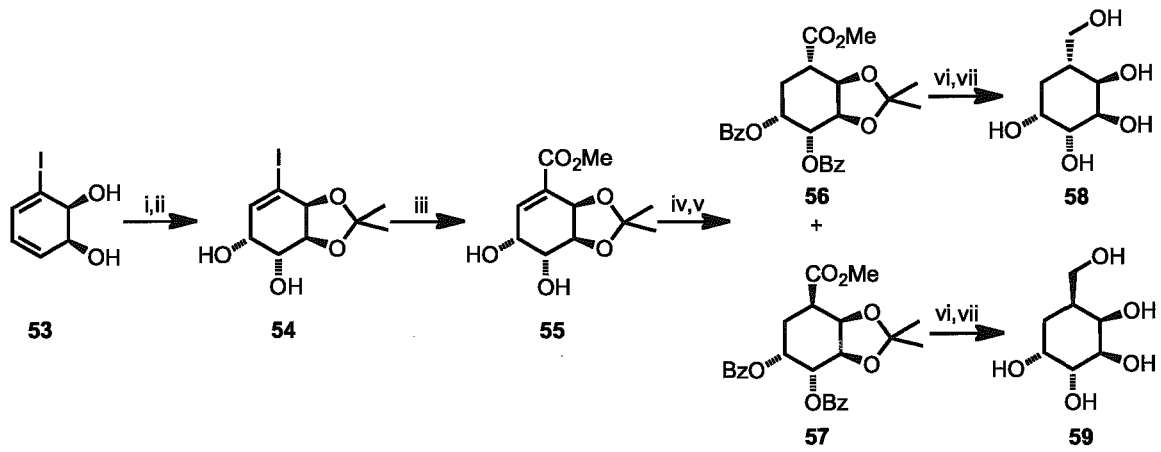
Reagents and conditions: i) 19 kbar (70%); ii) DMP, *p*-TsOH, H_2O (90%); iii) LiHMDS, MeI, THF (quant.); iv) $LiALH_4$, THF, 0 °C – 50 °C (99%); v) NaH, CS_2, MeI, THF; vi) nBU_3SnH, AIBN, PhMe, reflux (50-57% over two steps); vii) AcOH, THF, H_2O, 60 °C (95%); viii) 4-NAc-TEMPO, *p*-TsOH, CH_2Cl_2, 0 °C (91%); ix) iPr_2NEt, MEMCl, CH_2Cl_2 (91%); x) *hv* (triplet), acetone (80%); xi) nBU_3SnH, AIBN, PhH (87%); xii) $NaBH_4$, MeOH; xiii) NaH, CS_2, MeI, THF; xiv) nBU_3SnH, AIBN, PhMe, reflux (83% over three steps); xv) PPTS, *t*BuOH, reflux (76%); xvi) PCC, CH_2Cl_2 (71%); xvii) $CH_3P^+Ph_3Br^-$, KHMDS, PhMe (quant.).

Scheme 6. Banwell's synthesis of the sequiterepene (-)-hirsutene **60**.

The cycloaddition adducts were separated by column chromatography and the resulting diol was protected as the acetonide. To install the *gem*-methyl groups the acetonide was subjected to KHMDS followed by a methyl iodide to give ketone **55**. Lithium aluminum hydride reduction of ketone **55** gave two epimeric alcohols, which were converted to the corresponding xanthates. Allowing for a Barton-McCombie deoxygenation sequence followed by acid hydrolysis of the acetonide to give diol **56**. Selective oxidation of the less hindered hydroxy group using the 4-acetamido-TEMPO and protection of the remaining alcohol afforded keonte **57**.

Subjecting ketone **57** to a triplet sensitized photolysis resulted in the desired oxa-di-π-methane rearrangement product **58**. Triquinane **59** was produced by reductive cleavage of the carbonyl-cyclopropyl group with tri-*n*-butlytin hydride. The ketone was reduced using sodium borohydride and deoxygenated using the same Barton-McCombi deoxygenation sequence. Deprotection of the β-methoxyethoxymethyl ether under acidic conditions followed by a PCC oxidation and finally a wittig reaction produced (-)-hirsutene **60**.

Boyd's application of *cis*-cyclohexadienediol has developed several routes to various pyranose carbasugars.[30] Two of which are carba-β-D-altropyranose **66** and carba-α-L-galactopyranose **67** dervied from iodobenzene metabolite **61** (Scheme **7**).



Reagents and conditions: i) DMP, *p*-TsOH (98%); ii) OsO4, NMO, acetone, H_2O (87%); iii) $Pd(OAc)_2$, CO (1 atm), NaOAc, MeOH (81%); iv) Rh/Al_2O_3, H_2 (55 psi), EtOH; v) BzCl, pyridine (**64** 28% over two steps; **65** 56% over two steps); vi) $LiAlH_4$, THF, reflux ; vii) TFA (**66** 67% over two steps; **67** 68% over two steps).

Scheme 7. Boyd's synthesis of carbasugars carba-β-D-altropyranose **66** and carba-α-L-galactopyranose **67**.

Protection of **61** as the acetonide allowed for the facially directed dihydroxylation using osmium tetraoxide to give vinyl iodide **62.** Conversion of the acetonide to the α,β unsaturated ester **63** was accomplished by palladium catalyzed carbonylation in the presence of methoxide. Catalytic hydrogenation of the unsaturated ester gave a mixture of diastereomers. This mixture of diastereomers was inseparable therefore they were converted to the benzoate ester **64** and **65** to allow for separation by preparative layer chromatography. For both series the same sequence of reducing all three esters with lithium aluminum hydride and acid catalyzed acetonide deprotection afforded the respective carbasugars.

2.2 Morphine Alkaloids

2.2.1 History

Opium has been used by mankind since prehistoric times. It was one of the first drugs discovered. The opium poppy (*Papaver somniferum*) was cultivated in the Tigris-Euphrates river system of lower Mesopotamia in 3400 BC by the Sumerians, the world's first civilization.[31] Researchers from the University of Pennsylvania, excavating around the ancient city of Nippur, discovered tablets describing the collection of poppy juice from plants they called "Gil Hul" translating as "joy plant".[32] The collection of secretions from the opium poppy was also performed by the Assyrainas who named the juice collected "arat-pa-pal". Which some have speculated that the latin word "Papver" (botanical genus of the opium poppy) is derived from this term.[33] The spread of opium out of Mesopotamia was sparked by the conquest of the Assyria and Babylonia by the Persians around the

sixth century BC. One of the oldest known medical texts, the *Ebers Papyrus* dating back to 1552 BC, contains the 700 remedies, which include opium in their treatment.[34]

Between the 11th and the 13th centuries, medical uses of the opium poppy was introduced to the Chinese by the Arab traders.[33] However, opium was used chiefly by the elite until the introduction of smoking tobacco by European sailors in the 15th century. When the Ming emperor, Tsung Cen, banned the use of tobacco the Chinese people responded by mixing opium with tobacco for smoking in special pipes. By the end of the century approximately 25 percent of the population was smoking pure opium and thus historically opium use became synonymous with China.[34]

In the 18th century, the British Empire had a growing trade deficits with China. Thus the British Empire and the British East India Company responded by supplying opium to China to avoided bankruptcy. The Chinese responded by prohibiting the sales and use of opium. After the ban, British smugglers increased opium exports from 15 tons to 75 tons in less than 45 years.[35] The continued illegal import of opium caused tensions between the east and west which resulted in two conflicts known as the Opium Wars. Despite China losing in both conflicts the opium trade waned because of an anti-opium movement, as well as the British Empire became less dependent on the revenue from the sales of opium.[34] Because of this trade opium spread around the world but at the end of the 19th century the use of raw opium was reduced, as the active components of opium were isolated. The use of raw opium still continues today around the world, but not to the extent of purified and extracted alkaloids from opium.[36]

Opium is the air-dried exudate collected from lancing the unripen seed pods of *Papaver somniferum.*[33] The collected residue contains approximately 10-15% morphine **68**, 3-4% codeine **70**, 1-7% narcotine **72**, 0.5-1% papaverine **71** and 0.1-2% thebaine **70** as shown in figure 7.[37]

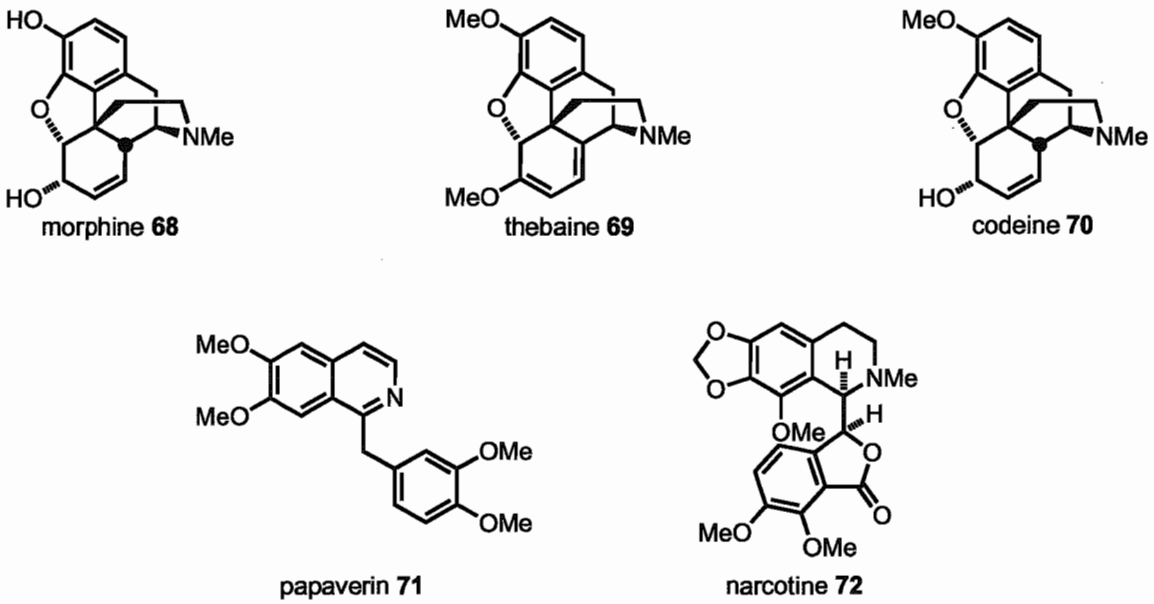


Figure 7. Naturally occurring opium alkaloids.

In 1806, pharamacist Friedrich Wilhelm Sertürner isolated the alkaloid morphine **68** from raw opium.[38-39] Sertürner coined the name "morphine" after Greek god Morpheus, God of Dreams. Shortly after the isolation of morphine, the structural elucidation began and early studies by Liebig and Laurent, in 1847, correctly determined the empirical formula as $C_{17}H_{19}NO_3$.[40] Wright is credited with the most important work in the elucidation of morphine's oxygenation.[41-42] This was followed by the establishment of the oxygenated phenanthrene core by degradation studies completed by Greichten, Hofmann, and Pschorr.[43-47] In 1952, the correct structure of morphine was proposed by Robinson[48] and confirmed by

the first total synthesis by Gates in 1952.[49] The absolute configuration of morphine was completed by MacKay and Hodgkin with the advent of X-ray diffraction analysis.[50] The complete story of isolation, structure elucidation and synthesis of morphine spans more than 150 years and is the subject of several reviews.[51-52] These accomplishments defined the early beginnings of modern organic chemistry and should be viewed as standards of sound thought and science.

2.2.2 Biosynthesis of morphine alkaloids

The biosynthesis of morphine and congeners have been elucidated as shown in figure 8.[53-54] All of the carbon atoms of morphine core come from two L-tyrosine **73** molecules which have "dimerised". In the first stage of biosyntheis, one molecule of tyrosine is converted into dopamine **74** by two enzymes, a tyrosine decarboxylase and a phenol oxidase. The second molecule of tyrosine **73** is converted to *p*-hyrdoxyphenylacetaldehyde **75** by the action of a transaminase followed by the decarboxylation.

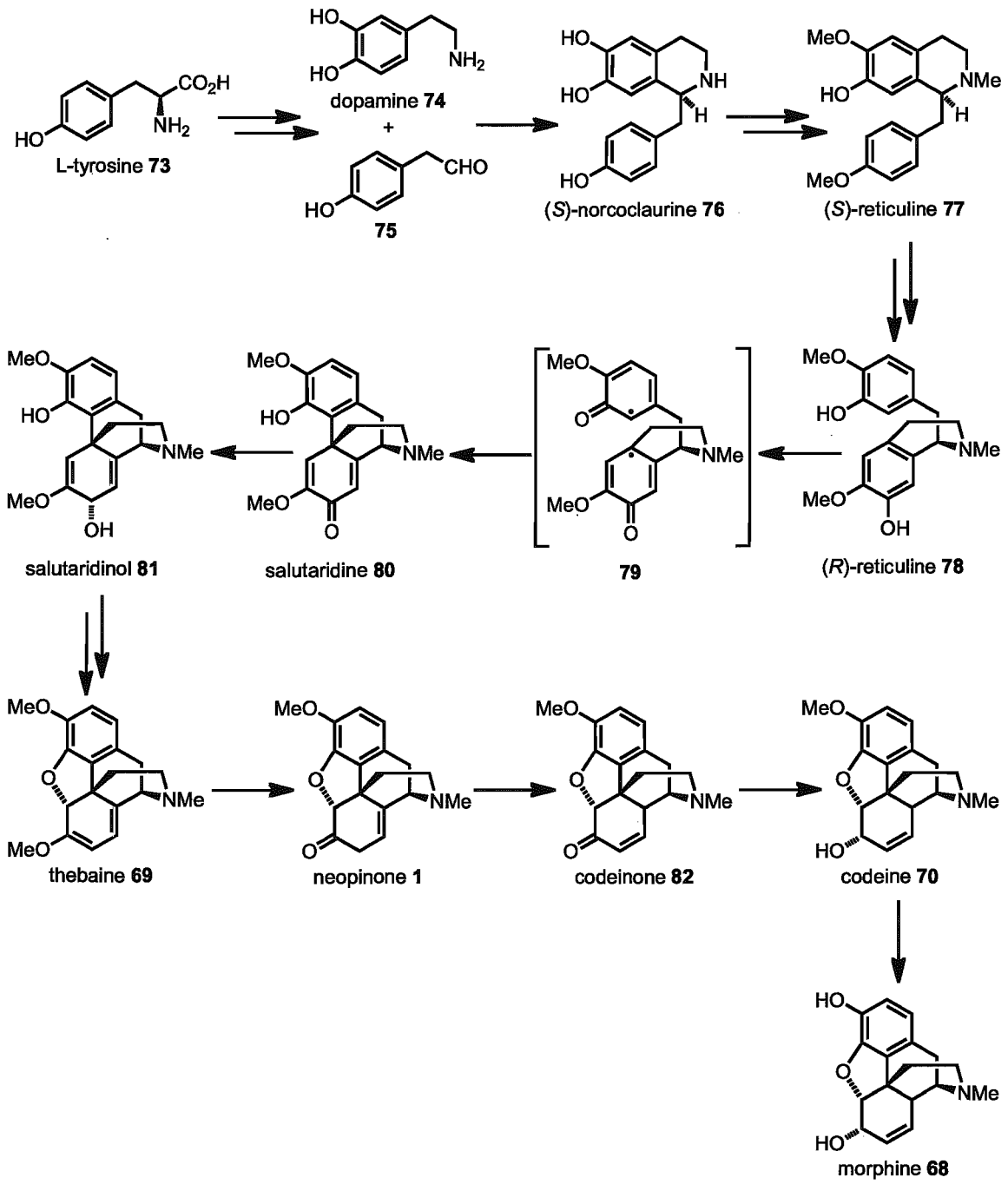


Figure 8. Biosynthesis of morphine.

These two pieces are coupled together by (*S*)-norcoclaurine synthase via a Pictet-Spengler type reaction to form (*S*)-norcoclaurine **76**. Oxidation followed by methylation give (*S*)-reticuline **77**, which is then epimerized by an oxidation

reduction sequence by 1,2-dehydroreticulinium reductase to give (*R*)-reticuline **78**.[55] An oxidative phenol coupling catalyzed by a microsomal NADPH-dependent cytochrome P450 couples carbon 12 to carbon 13 (morphine numbering) to give salutaridine **80**, which establishes stereospecifically the quaternary center of the morphine skeleton. Salutaridine **80** is then reduced to form salutaridinol **81** and thenacetylated by salutaridinol 7-*O*-acetyltransferase. The phenolic hydroxyl displaces the allylic acetate by S_N2' reaction yielding thebaine **69**. Thebaine is demethylated to form neopinone **1** by a recently discovered enzyeme thebaine 6-*O*-demethylase.[56] Neopinone **1** which exists in an equilibrium with codeinone **82** is then reduced by codeinone reductase resulting in codeine **70** which in turn is demethylated by codeine-*O*-demethylase to morphine **68**.[37, 57]

The biosynthetic pathway of the production of morphine is considered to be well understood.[54] However the existence of thebaine oripavine poppy 1 (*top1*) mutant poppy which produces oripavine and thebaine **69** and not morphine **68** and codeine **70** suggest the presence of an alternative biosynthetic pathway for the conversion of theabine **69** to morphine **68**.[58] It was proposed the mutation of the enzyme responsible for demethylation of the C-6 oxygen of thebaine **69** in the poppy mutant top1 is responsible for the break in the morphine biosynthetic pathway and thus explains the accumulation of oripavine and thebaine **69**.[59]

2.2.3 Pharmacology

Opioids constitute one of the oldest drugs known to man and are among the most effective treatments available for pain relief.[60] Morphine **68** and other

congeners have major effects on the central nervous system which are responsible lowering the brain's awareness of pain. However, these benefits can be outweighed by the side effects of opioids; which include, but are not limited to, respiratory suppression, constipation, convulsions, hallucinations and physical dependence.[61]

In 1954, Beckett and Casy attempted to explain the effects of opiods on the central nervous system.[62] They proposed that morphine and its congeners required specific binding interactions for their activity. These included a positively charged nitrogen, correctly orientated aromatic ring, a C-3 phenol and a binding pocket to allow for the ethylene bridge. By the late 1960s, Goldstein postulated that the different activities of opioid agonists, antagonists and mixed agonists-antagonists were a result of multiple opiate receptors. At the time their labors to prove this theory failed because of the poor availability of radiolabeled opiates.[63] However, in 1973 three groups simultaneously proved Goldstein's hypothesis by indentifying multiple opioid receptors.[64-66] Questions arose whether morphine was not an endogenous opioid ligand. This was confirmed by the work of Kosterlitz in 1975, who showed mammalian brain extracts contained substances that inhibit the acetylcholine release from nerves.[67] The agents responsible for this act were identified as met-enkephalin **86** (Tyr-Gly-Gly-Phe-Met) and Leu-enkephalin **87** (Tyr-Gly-Gly-Phe-Leu)[68] (figure 9). Other peptidic endogenous opiod receptor ligands were identified varying in length from 5 to 33 amino acids and are known as endorphins (**endo**genous m**orphine**).[60]

Spread throughout the central nervous system is the presences of opioid receptors. There are three commonly recognized opioid receptors: μ, κ and δ

receptors, all of which exhibit analgesic properties but to various levels. All of these receptors show structural homology with each other; however, they act through different modes of action.[69]

Agonist activation of the μ-recpetor results in analgesia as well as side effects of euphoria, respiratory depression, constipation and addiction. Opioid binding to the μ-receptor induces a conformational change that opens an ion channel. This allows the potassium ions to flow out of the cell resulting in an increase of membrane polarization. This results in a decrease in the influx of calcium ions causing synaptic inhibition.[33] Endogenous ligands include enkephalins and β-endorphins, while morphine is a standard of an exogeneous opiod. Opioid abuse can be treated with naloxone **84** and naltrexone **83**, both of which are antagonists of the μ-receptor.

Activation of κ-receptor is directly associated with calcium channels. Binding closes the calcium channel and therefore prevents the release of neurotransmitters, as calcium is required for this to occur. The kappa receptors are related to non-thermal pain stimuli where as with the μ-receptor all pain messages are inhibited.[70] It is interesting to note that κ-agonists do not show the addictive and physical dependence as that of μ-agonists and thus could show promise of a "safe" analgesic.[69] However clinical trials of κ-agonists have shown dysphoric and psychotomimetic effects.[71]

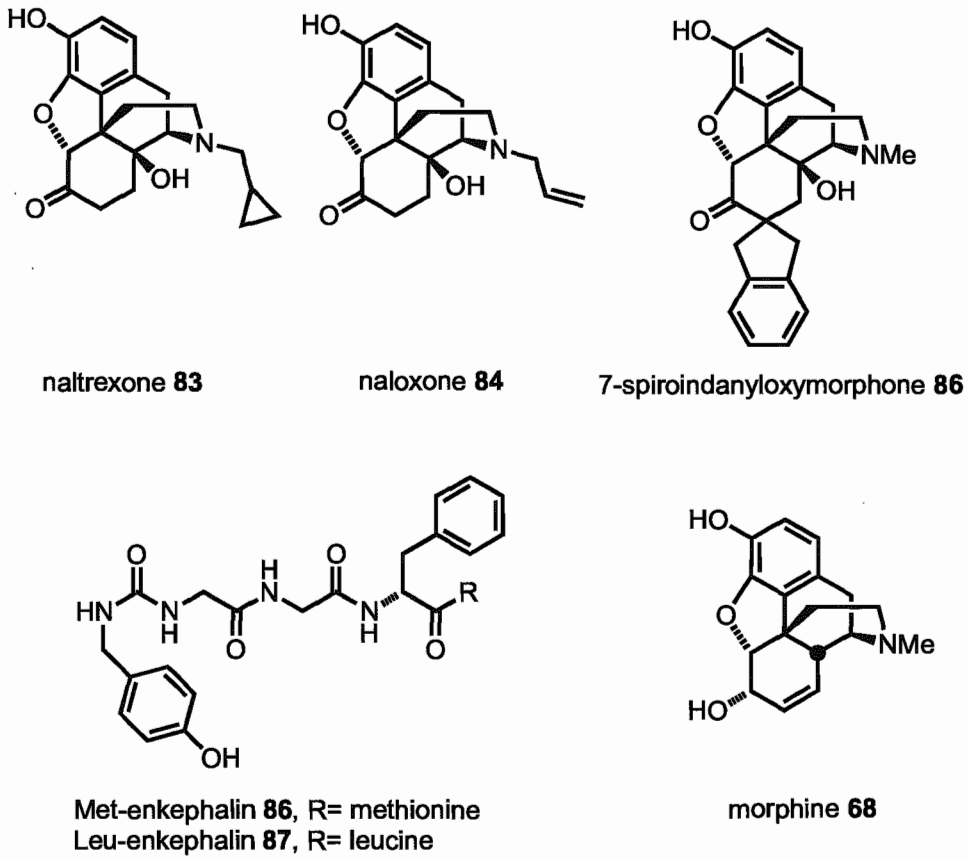
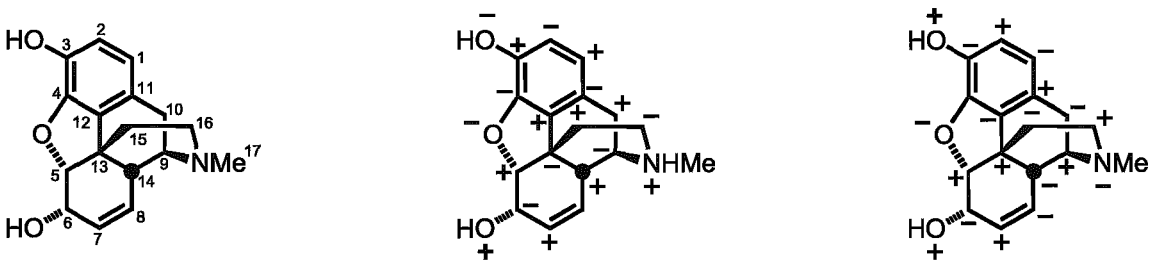


Figure 9. Selective opioid receptor agonists and antagonists.

The δ-receptor is a G-protein linked receptor. When an agonist binds the protein under goes a conformation change resulting in the fragmentation of the messenger G_i-protein. This fragmentation inhibits the membrane bound adenylate cyclase from produce cAMP. cAMP is required for the transmission of pain singals and therefore stops the signal.[60] Endogenous agonist of δ-receptors are Met and Leu enkephalins **86** and **87** and an excellent example of an exogenous agonist is 7-spiroindanyloxymorphone **86**.[72]

2.2.4 Selected Syntheses[73]

Morphine and its congeners have attracted the attention of chemists for well over 200 years. Since the first synthesis of morphine by Gates and Tschudi in 1952 the interest in morphine as a synthetic target has not waned.[1, 57, 74-75] Despite morphine's small size, it is complex target because of the pentacyclic framework, five contiguous stereocenters, the C-4 C-5 ether bridge. Of considerable challenge is the completely dissonant, incorrect polarity assignment of an electronegative atom or two adjacent like charges, assemblely of the 17 carbons of morphine (figure 10).[1] The following sections highlights a selection of the efforts towards the total synthesis of morphine alkaloids to date.



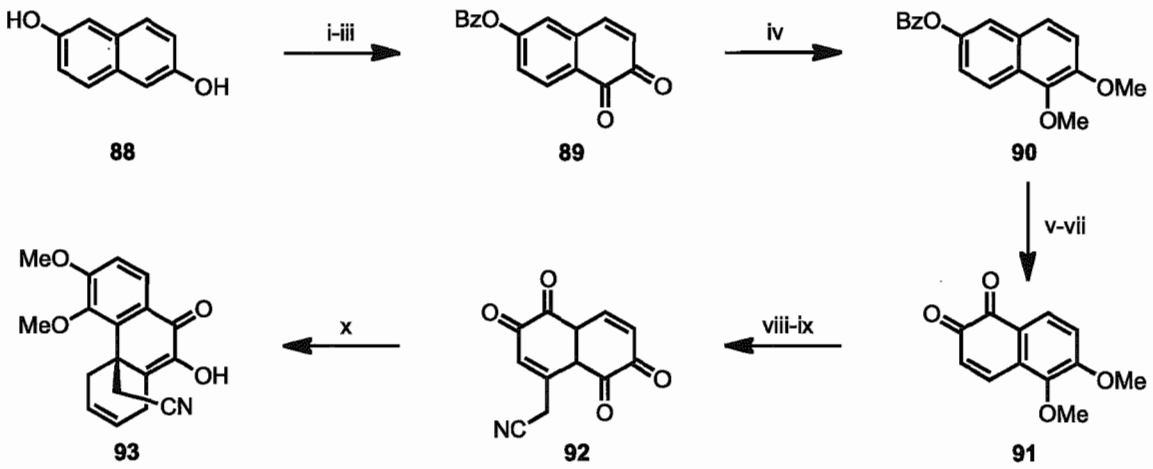
morphine **68**

Figure 10. Dissonant relationship in morphine connectivity

Gates (1952)[49, 76]

In 1952, Gates and Tschudi published the first total synthesis of morphine as a two-page communication, confirming Robinson's proposed structure.[49] The full disclosure of the synthesis appeared four years later.[76] Their synthesis required 24 steps to construct morphine **68** from 2,6-dihydroxynapthalene **88** in an overall yield

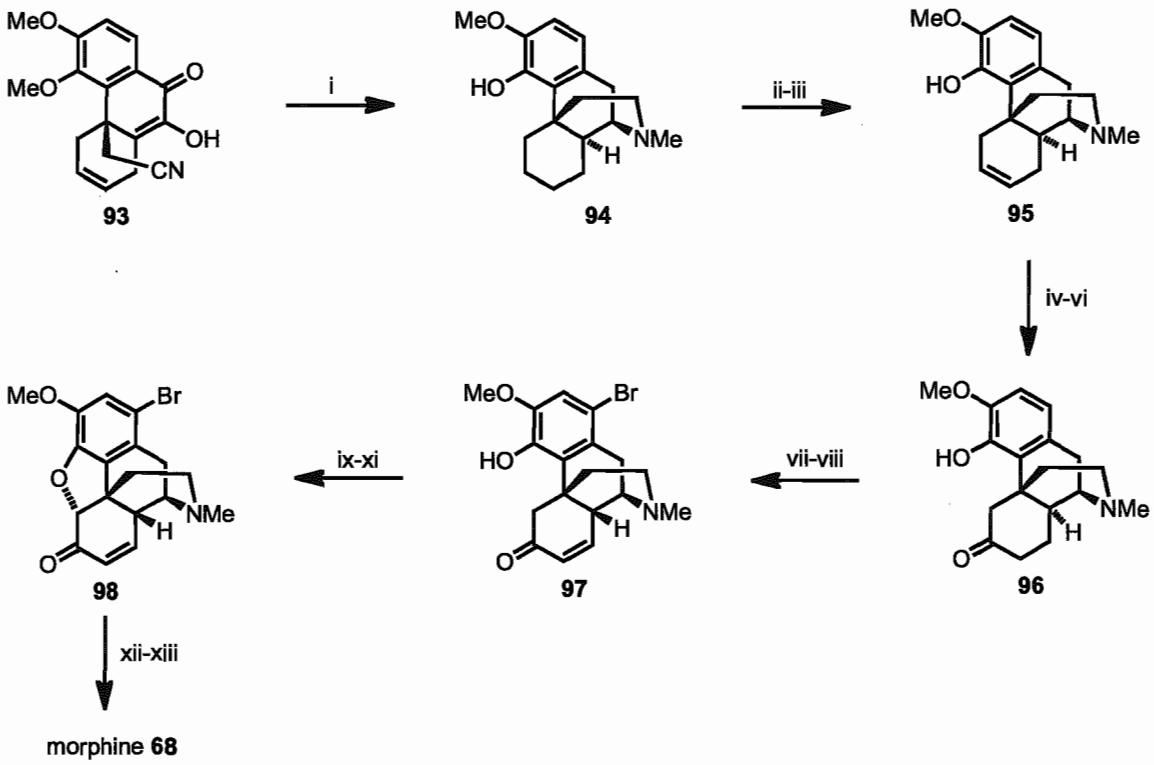
of 0.01%. The synthesis begins with the conversion of 2,6-dihydroxynapthalene **88** by a nitrosation/ reduction/ oxidation sequence into the quinone **89** (scheme 10).



Reagents and conditions: (i) BzCl, pyridine, dioxane; (ii) $NaNO_2$, AcOH; (iii) a) Pd/C, H_2, AcOH; b)$FeCl_3$; (iv) a) SO_2; b) $(MeO)_2SO_2/K_2CO_3$; (v) KOH; (vi) $NaNO_2$, AcOH; (vii) a) Pd/C, H_2; b)$FeCl_3$; (viii) a) $NCCH_2CO_2Et$, EtOH, NEt_3; b)$K_3Fe(CN)_6$; (ix) KOH, MeOH; (x) 1,3-buatdiene, AcOH.

Scheme 9. Gates' synthesis of the Diels-Alder product **93**

This allowed for the installation of two unique 1,2-dioxygen functionalities on both rings. Michael type addition of ethyl cyanoacetate to **91** followed by a oxidation decarboxylation sequence resulted in nitrile **92.** The installation of the C-ring was performed by a Diels-Alder reaction with 1,3-butadiene giving **93.** By performing reductive cyclization using copper chromite under "mild conditions" (130 °C, 27 atm of hydrogen), as reported by the authors, the D-ring was closed to form the keto amide (scheme 10).



Reagents and conditions: (i) 27 atm H_2, CuO, Cr_2O_3, EtOH, 130°C (50%); ii) KOH, N_2H_4 (90%); iii) a) NaH, MeI; b) $LiAlH_4$ (54%); iv) H_2SO_4, H_2O (28%); v) KOH, ethylene glycol (54%); vi) KO_tBu, Ph_2CO (89%); vii) Br_2, AcOH, 2,4-DNPH (41%); viii) HCl; ix) H_2, PtO_2; x) Br_2, AcOH, 2,4-DNPH (26%); xi) HCl, acetone (27%); xii) $LiAlH_4$ (quant.); xiii) Py•HCl, 220°C (35%).

Scheme 10. Gate's final transformations to morphine **68**.

Gates states the course of the reductive cyclization leading to the tetracyclic skeleton "was far from clear". Wolff-Kishner reduction of the ketoamine followed by methylation and reduction with LAH afforded *N*-methyl piperidine **94** containing all the necessary carbons of morphine. A resolution of **94** was performed by crystallizations with D-dinitrobenzoyltartaric acid. Unfortunately this provided the correct stereochemistry at C-9 and C-13 but the epimer at C-14. Hydration of C-6 was performed using dilute sulfuric acid. Selective demethylation of the proximal methyl ether followed by oxidation furnished ketone **96**. To resolve the

stereochemistry at C-14, compound **96** was treated with two equivalents of bromine followed by the hydrazone formation with 2,4-DNPH as shown in figure 11. This introduced an α,β-unsaturation, as seen in compound **100**, which allowed for the equilibrium of the hydrogen at C-14 to the more stable *cis* fused ring system **102**. Acid meditated hydrolysis followed by hydrogenation to reduce the α,β-unsaturation formed by the introduction of the hydrazone gave ketone **97** with the correct stereochemistry at C-14. Closure of the E-ring was accomplished by bromination of **97** followed by treatment with 2,4-DNPH and installed the α,β-unsaturation. Gates finished his synthesis with hydrolysis of the hydrazone followed by reduction to give codeine **70**. Follwing Rappoport's conditions for the demethylation of codeine completed the first synthesis of morphine **68**.[77]

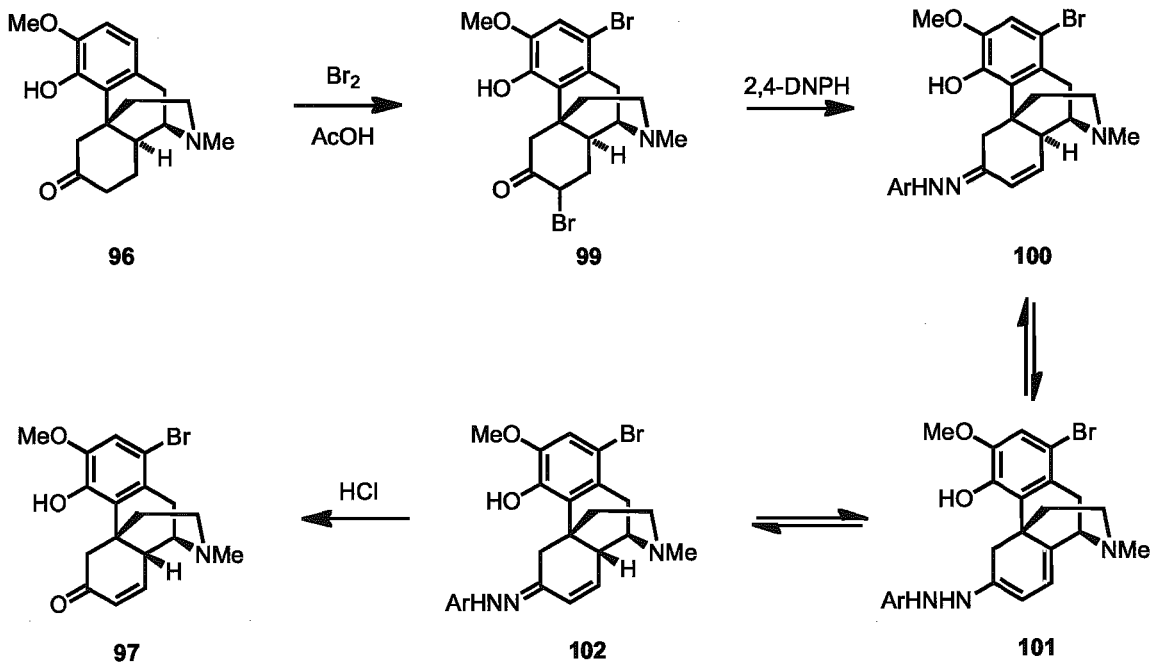
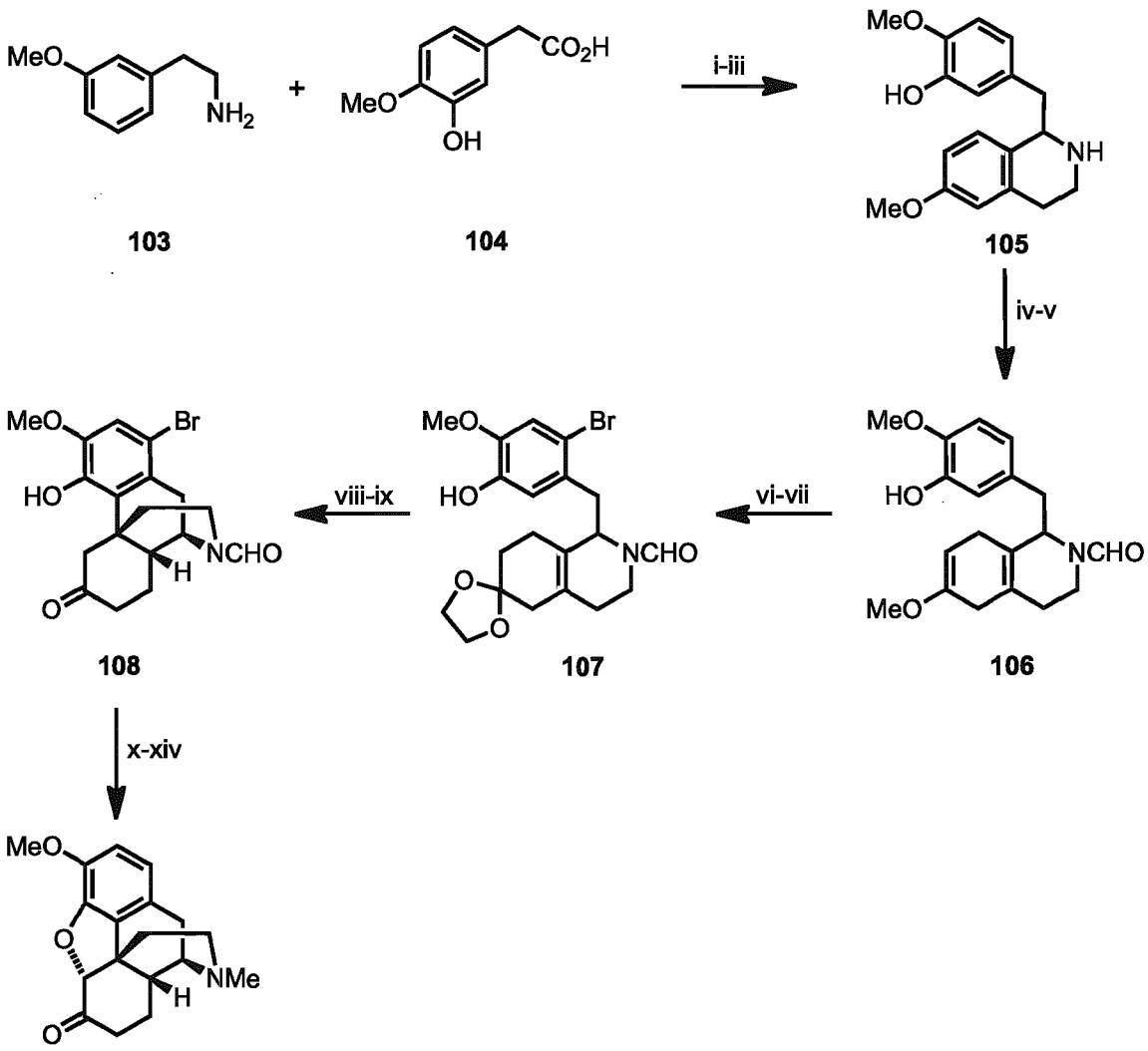


Figure 11. Epimerization of C-14.

Rice (1980)[78]

The formal syntheis of morphine **68**, completed by Rice in 1980, is arguably the most practical synthesis to date. The biomimetic approach allows for the synthesis of both the natural and unnatural enantiomers of hydrocodone **109**. The synthesis was completed with only six intermediates, no chromatography and the overall yield is an astounding 29%.

The synthesis begins with the condensation of amine **103** and acid **104** followed by a Bischler-Napieralski reaction and treament of the resulting imine with sodium cyanoborohydride gave the cyclized amine **105** (scheme 11). Birch reduction followed by formylation with phenyl formate furnished **106.** Protection of the masked ketone with ethylene glycol and regioselective bromination gave the cyclization precursor **107**. Acidic hydrolysis of the ketal followed by a hydrogen fluoride mediated Grewe cyclization provided the tetracyclic core of morphine in 60%. Mild hydrolysis of the formamide **108** followed by α-bromination of the ketone initiated the E-ring closure. Hydrogenation in a mixture of acetic acid and formaldehyde removed the aryl bromide and methylated the secondary amine providing hydorcodone **109**, a formal synthesis of morphine **68**.

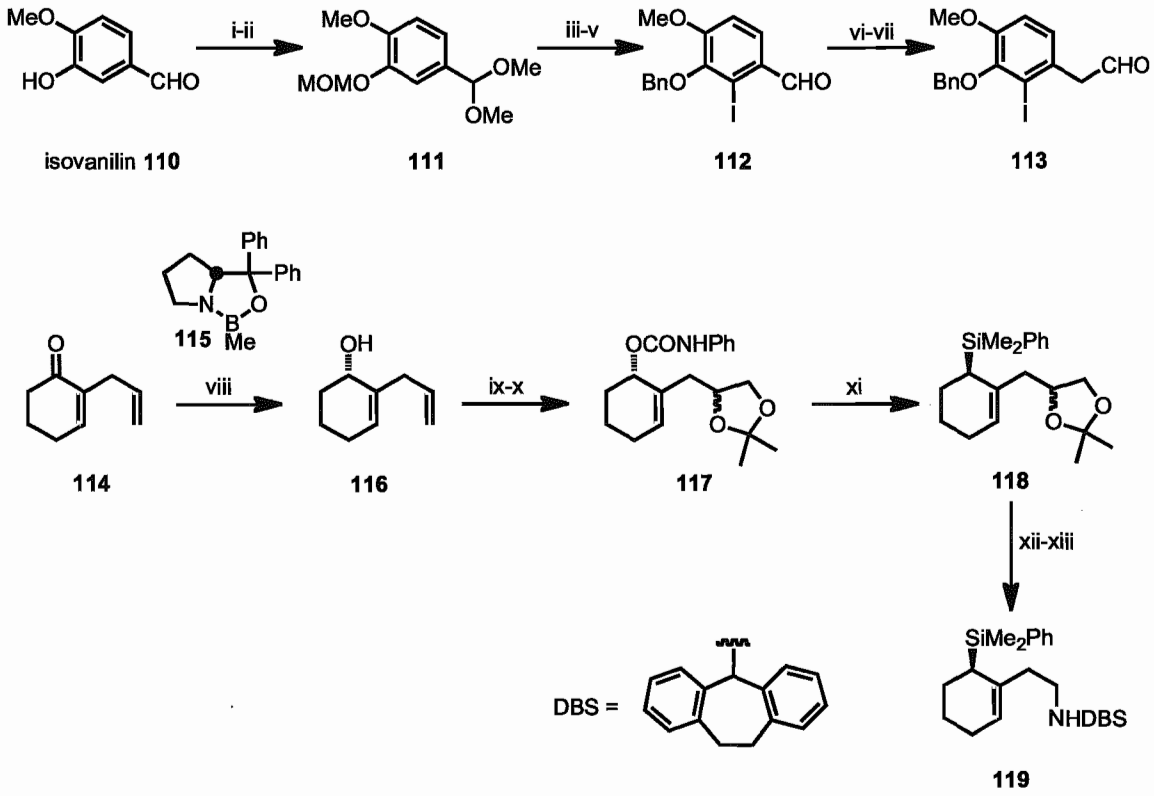


Reagents and conditions: i) 200°C (95%); ii) $POCl_3$, MeCN; iii) $NaCNBH_4$, MeOH (86%); iv) Li, NH_3, THF, *tert*-BuOH (90%); v) PhOCHO, EtOH (94%); vi) ethylene glycol, $MESO_3H$, THF; vii) NBA (88%); viii) $HCO_2H \bullet H_2O$ (90%); ix) $NH_4 \bullet HF$, CF_3SO_3H (60%); x) MeOH, HCl (92%); xi) H_2, Pd/C, AcOH, HCHO; xii) Br_2, AcOH; xiii) NaOH, $CHCl_3$; xiv) H_2, AcOH, HCHO (79% over 4 steps)

Scheme 11. Rice's synthesis of hydrocodone **109**.

Overman (1993)[79]

Overman's synthesis of morphine was the first published enantiodivergent approach to morphine that did not involve resolution of intermediates. The key step to overman's synthesis was the use of iminium ion-allylsilane cyclization followed by an intramolecular Heck reaction. The synthesis starts with the preparation of the A-ring from isovanilin **110** with the protection of the phenol and the aldehyde to give the ketal **111** (Scheme 12).



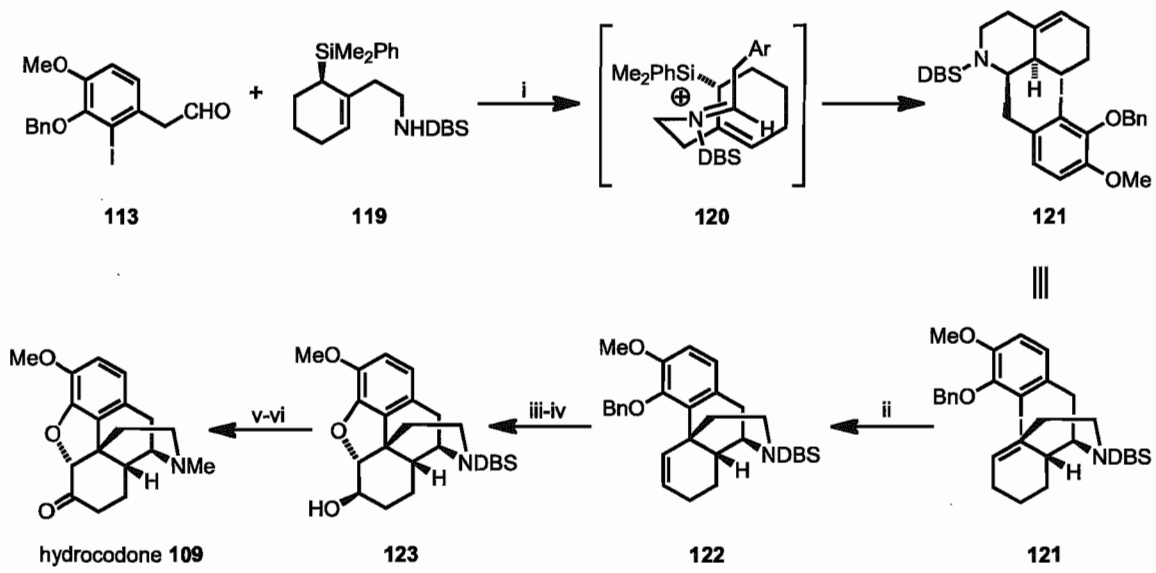
Reagents and conditions: i) $HC(OMe)_3$, HCl; ii) NaH, $ClCH_2OMe$; iii) *n*-BuLi, I_2 (80%); iv) 6N HCl; v) BnBr, K_2CO_3 (97%); vi) CH_2SMe_2 (91%); vii) $BF_3{\bullet}OEt_2$, THF (92%); viii) **115**, catechol borane (93%); ix) PhNCO (93%); x) OsO_4, acetone, HCl (78%); xi) a) *n*-BuLi, THF, -30°C; b) $CuI(PPh_3)_2$, 0°C; c) $PhMe_2SiLi$, 0°C (81%); xii) *p*-TsOH, MeOH, $NaIO_4$; xiii) DBS-NH_2, $NaCNBH_3$ (88%).

Scheme 12. Overman's preparation of morphine precursors **113** and **119**.

Lithiation of compound **111** followed by quenching with iodine, and acidic hydrolysis and reprotection as the benzyl ether afforded aldehyde **112**. Treatment of the aldehyde with dimethylsulfonium methylide followed by Lewis catalyzed rearrangement of the resulting epoxide provided the desired aldehyde **113**.

The coupling partner was prepared from 2-allylcyclohex-2-enone **114** by enantioselective reduction with catecholborane in the presence of a chiral catalyst, (*R*)-oxazaborolidine **115**, to yield (*S*)-cyclohexenol **116** in 96% ee. Condensation of the alcohol with phenyl isocyanate followed by selective catalytic dihydroxylation of the terminal olefin and protection provided the acetonide **117**. Treatment of compound **117** with *n*-butyl lithium, $CuI(PPH_3)_2$ and $PhMe_2SiLi$ allowed for the [3,3] sigmatropic rearrangement followed by the S_N2' displacement of the allylic carbamate resulting in the formation of the allylsilane **118**. Hydrolysis of the acetonide followed by periodate cleavage of the diol resulted in the desired aldehyde. Which upon treatment with dibenzosurberylamine followed by reduction with sodiumborohydride gave coupling precursor **119**.

Condensation of the aldehyde **113** with the amine **119** in the presence of zinc(II) iodide followed by the aforementioned iminium ion-allylsilane cyclization provided the desired octahydroiosquinoline **121** (scheme 13). The preferential approach of the (*E*)-iminium ion intermediate **120** from the face opposite to that of the allylsilane results in the high diastereoselectivity of 20:1.



Reagents and conditions: i) ZnI_2, EtOH, 60°C (82%); ii) $Pd(TFA)_2(PPh_3)_2$, 1,2,2,6,6-pentamethylpiperidine, toluene (60%); iii)$BF_3 \cdot OEt_2$, EtSH (79%); iii) CSA, 3,5-dinitroperoxybenzoic acid (60%); iv) TPAP, NMO (86%); v) H_2, $Pd(OH)_2$, HCHO (80%).

Scheme 13. Overman's formal synthesis of hydrocodone **109**.

Sequential Heck cyclization resulted in the unsaturated compound **122**. Deprotection of the benzyl ether followed by treatment with camphorsulfonic acid and 3,5-dinitroperoxybenzoic acid allowed for the closure of the ether bridge between C-4 and C-5. The formal synthesis of morphine was concluded by oxidation of the alcohol **123** and hydrogenation of the DBS group providing hydrocodone **109**.

Fukuyama (2006)[80]

In 2006, Fukuyama disclosed his synthesis of *rac*-morphine. The approach featured a Tsuji-Trost coupling[81-82] followed by a Heck coupling, which was employed in Trost's synthesis of morphine[83-84], furnished the tricyclic core of morphine. The closure of the penatcyclic ring systems was finished by a Mannich-

type reaction as seen in Figure 12. The synthesis was performed using a racemic epoxide, however generation of a chiral epoxide **128** could furnish access to the natural and unnatural series of morphine.

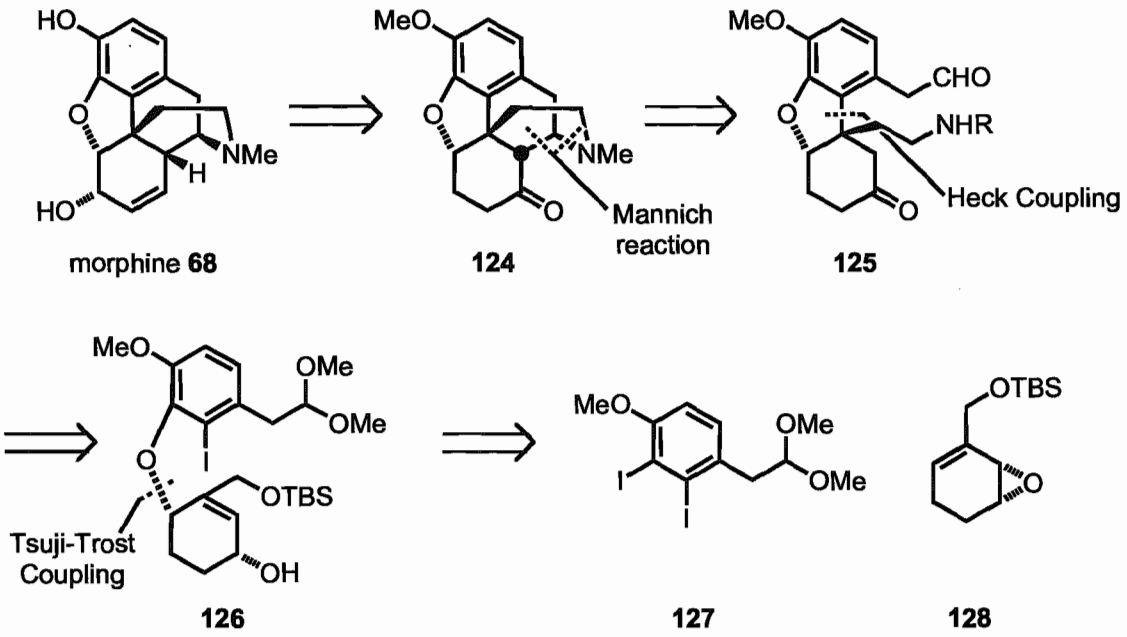
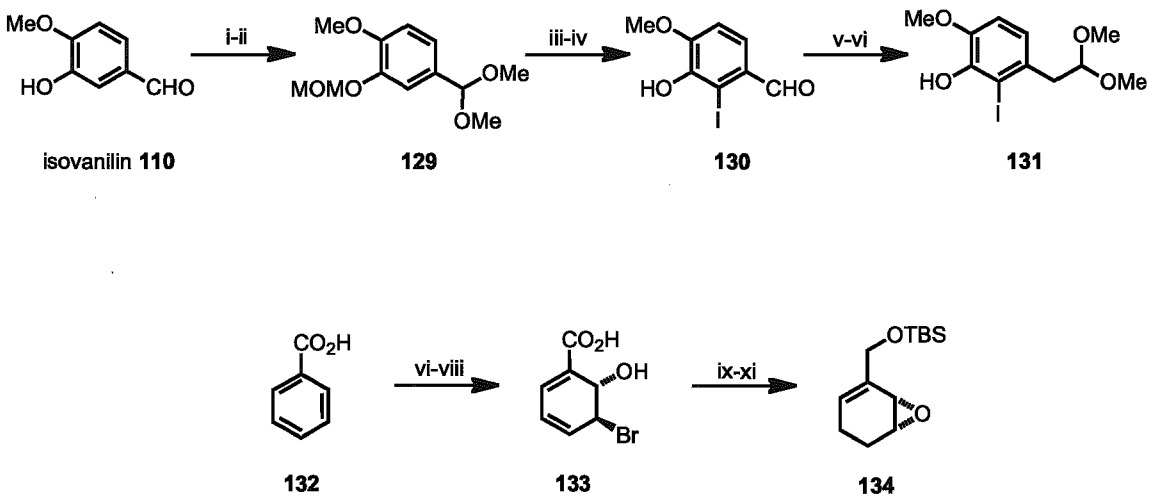


Figure 12. Fukuyama's strategy for the synthesis of morphine **68**.[80]

Similar to that of Overman's synthesis, Fukuyama's starts with the conversion isovanillin **110** to the aryl iodide **130** by protection of the phenol and aldehyde followed by iodination (Scheme 14). Acidic hydrolysis of the acetal and subsequent olefin elongation via Wittig reaction furnished the homoisovanilin. Deprotection of the phenol via hydrolysis in methanol provided the A-ring coupling partner **131**.

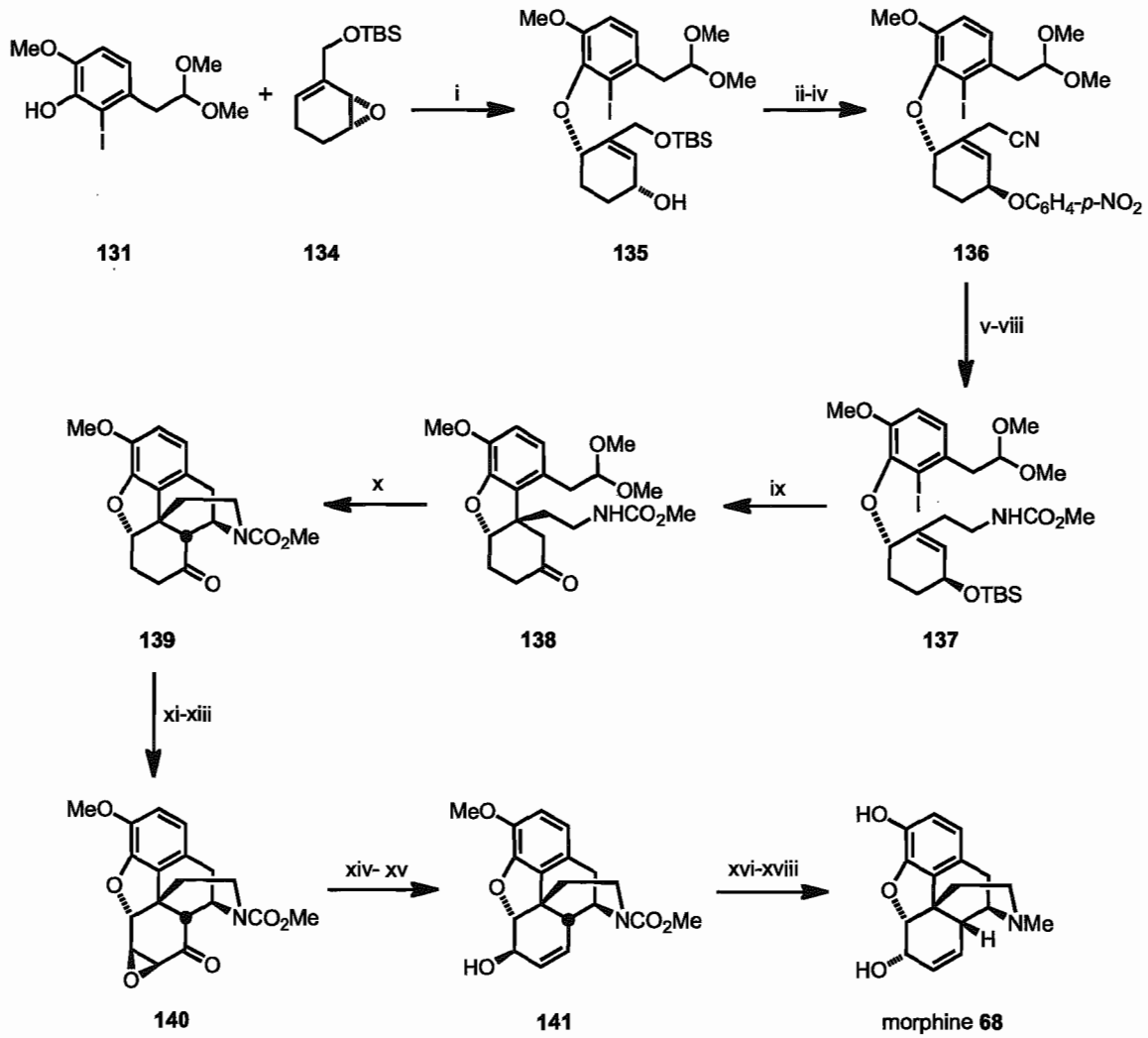


Reagents and conditions: i) MOMCl, *i*Pr_2NEt; ii) CSA, $HC(OMe)_3$; iii) *n*-BuLi, I_2 (72% over 3 steps); iv) AcOH, THF, H_2O (89%); v) $MeOCH_2PPh_3Cl$, NaHMDS, THF (95%); vi) HCl, MeOH, 40 °C (96%); vi) Na, NH_3, EtOH, -78 °C; vii) a) AcCl, MeOH; b) NaOMe; viii) NBS, H_2O, DMSO (62% over 3 steps); ix) DIBAL, CH_2Cl_2, 0 °C (73%); x) NaOMe, MeOH; xi) TBSCl, imidazole, CH_2Cl_2 (61% over two steps).

Scheme 14. Preparation of coupling partners **131** and **134**.

Synthesis of the epoxide **134**, which was previously reported by Fukuyama in his synthesis of strychnine,[85] started with the Birch reduction of benzoic acid **132** followed by isomerization of the double bond and treatment with *N*-bromosuccinimide to form the bromohydrin **133**. Reduction of the ester and treatment under basic conditions afforded the desired epoxide. Protection of the alcohol as the silyl ether furnished the desired coupling partner **134**. A palladium mediated Tsuji-Trost coupling afforded the ether **135** (scheme 15). Inversion of the allylic alcohol was performed with *p*-nitrobenzoic acid under Mitsunobu conditions followed by deprotection of the silyl ether and a second Mitsunobu reaction using 2-hydroxy-2-methylpropanenitrile gave the desired nitrile **136**. Hydrolysis of the ester and protection as the silyl ether was performed prior to reduction of the

nitrile. To avoid reductive cleavage of the aryl iodide the nitrile was treated with diisobutylaluminium hydride followed by the addition of sodium hydride in MeOH to furnish the amine, which was then protected with methyl chloroformate to furnish the amide **137**. With amide **137** in hand, the crucial intramolecular Heck cyclization was performed to give the silyl enol ether, which was deprotected in one pot to provide the ketone **138.** To finish the pentacyclic core system of morphine, Fukuyama heated ketal **138** with methanolic hydrogen chloride which proceeded smoothly through a Mannich-type reaction to close the C9-C-14 bond. Ketone **137** was converted to the enone via conversion to the silyl enol ether followed by treatment with palladium(II) acetate, conditions reported by Ito and Saegusa[86]. This enone was then oxidized to the corresponding epoxide **140** with hydrogen peroxide. Reduction of the ketone with sodium borohydride resulted in the alcohol, which was converted to the thiocarbamate. Treatment with tributyltin hydride induced the opening of the epoxide and Barton-McCombie dexoygenation to provide the allylic alcohol. To obtain the correct chemistry at C-6 a two step oxidation/reduction sequence where the carbamate was also reduced to the tertiary amine giving codeine **70**. Following Rice's procedure for *O*-demythlation using boron tribromide furnished morphine **68**.[87]



Reagents and conditions: i) $Pd_2(dba)_3$, P(2-furyl)$_3$, MeCN (91%); ii) *p*-nitrobenzoic acid, DEAD, PPh_3, toluene, 0 °C (90%); iii) CSA, MeOH (94%); iv) 2-hydroxy-2-methylpropanenitrile, DEAD, PPh_3, toluene, 0 °C v) $LiBH_4$, Et_2O, MeOH, 0 °C (95% over 2 steps); vi) TBSCl, imidazole (96%); vii) a) DIABLH, CH_2Cl_2 -78 °C; b) $NaBH_4$, MeOH, -78 °C; c) $ClCO_2Me$, K_2CO_3 (94%); viii) a) $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, NEt_3, MeCN; b) TBAF (87%); ix) HCl, MeOH, reflux (94%); x) TMSCl, LiHMDS, THF, 0 °C xi) $Pd(OAc)_2$, MeCN (92% over two steps) xii) H_2O_2, H_2O, NaOH, MeCN, 0 °C (91%); xiii) $NaBH_4$, MeOH, CH_2Cl_2, 0 °C (91%); xiv) TCDI, DMAP, $ClCH_2CH_2Cl$, 60 °C; xv) Et_3B, *n*-Bu_3SNH, THF (48% over two steps); xvi) Dess-Martin periodinanel, CH_2Cl_2 (96%); xvii) $LiAlH_4$, THF (81%); xviii) BBr_3, CH_2Cl_2 (74%).

Scheme 15. Conclusion of Fukuyama's synthesis of morphine.

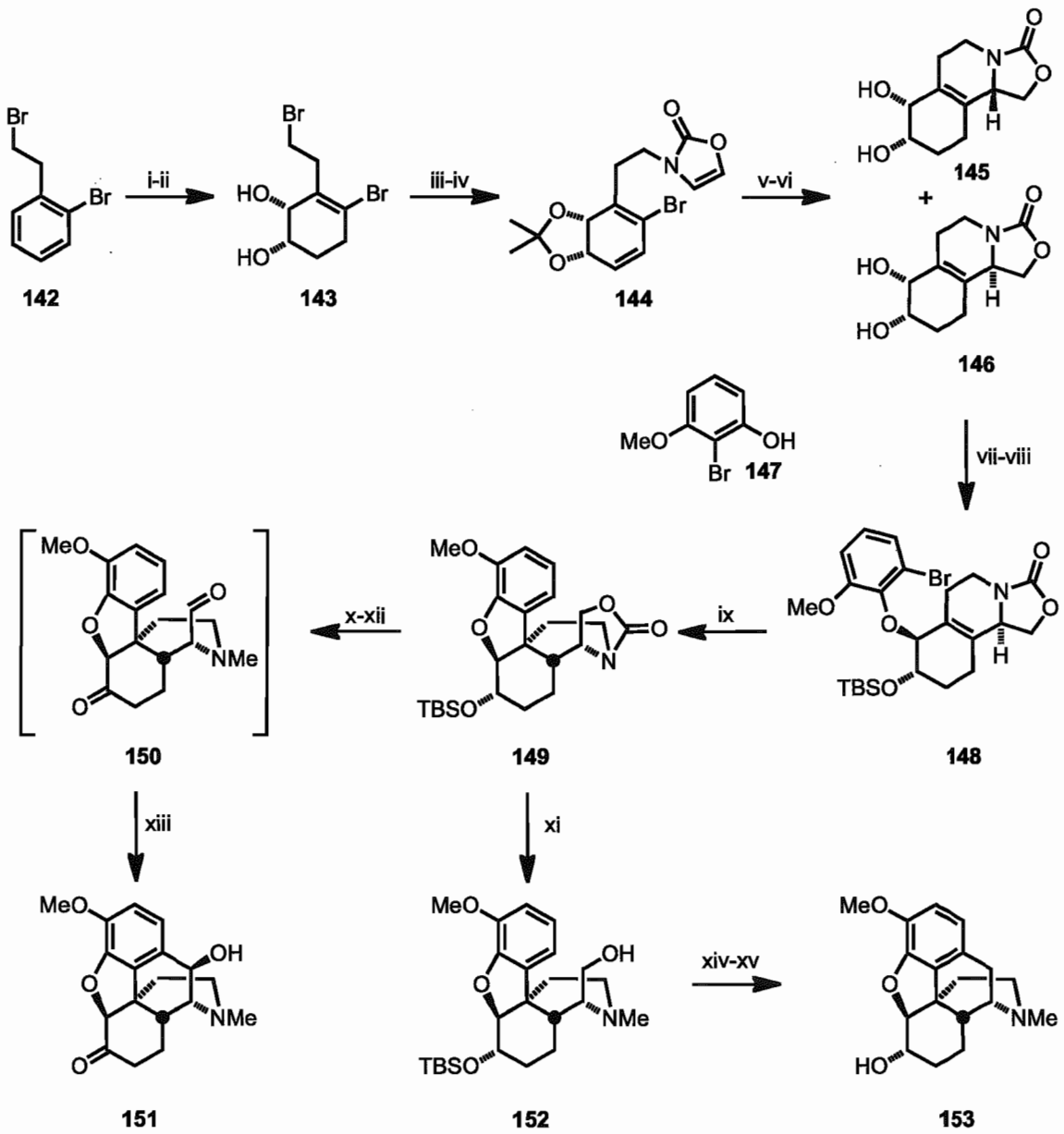
Hudlicky (1996 to present)

The Hudlicky group presented numerous approaches to morphine based on a wide range of unique strategies over the last 20 years. The common feature amoung these approaches have been the use of *cis*-cyclohexadienediols generated by enzymatic transformations of arenes. A brief review of Hudlicky's labors in the practical synthesis of morphine and its congeners will be presented in the following pages.

Radical cyclization approach[51-52, 74, 88-90]

Inspired by the work of Parker,[91-92] Hudlicky designed several radical cyclization approaches to morphine alkaloids. All of the approaches utilized the enzymatic *cis*-dihydroxylation of arenes as the source of chiral building blocks.

Hudlicky's first approach started with the 1,2-diol metabolite of *o*-bromo-β-bromoethylbenzene **142** (scheme 16). Diimide reduction of the distal olefin using potassium azodicarboxylate under acidic conditions gave diol **143**. Protection of the diols with ethylene glycol afforded the acetonide, which was followed by the subsitution of the alkyl bromide with oxazol-2(3H)-one produced the radical cyclization precursor **144**. Treatment of compound **144** with *n*-tributyltinhydride and AIBN followed by treatment with acid Dowex resin furnished a 2:1 mixture of octahydroisoquinolines **145** and **146**, in the favour of the undersired *epi*-C9 configuration.

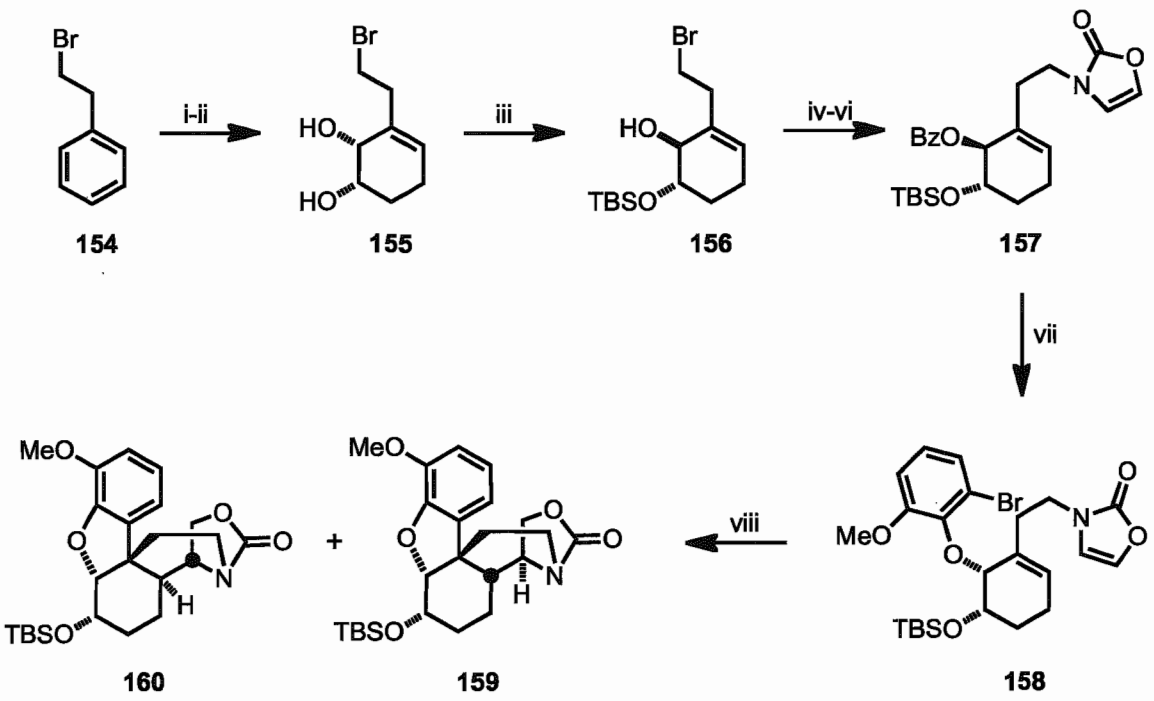


Reagents and conditions: i) *E.* coli JM109 (pTDG602) (0.2g/L); ii) PAD, AcOH, MeOH (50%); iii) 2,2-dimethoxypropane, *p*-TsOH (90%); iv) 2-oxazolidone, NaH, DMSO (38%); v) *n*-Bu_3SnH, AIBN, benzene, reflux (87%); vi) Dowex 50X8-100, MeOH (94%); vii) TBSOTf, *i*-Pr_2NEt, CH_2Cl_2 (85%) viii) **147**, DEAD, PPh_3, THF (94%); ix) *n*-Bu_3SnH, AIBN, benzene, reflux (47%); x) TBAF, THF (quant.) xi) DIBAL-H, CH_2Cl_2, 0 °C (87%) xii) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2 (66%); xiii) TFA (58%); xiv) MsCl, NEt_3, THF (87%); xv) $AlCl_3$, toluene, reflux.

Scheme 16. Hudlicky's synthesis of *ent*-morphinans **151** and **153**.

Protection of the homoallylic alcohol as the silyl ether followed by a Mitsunobu inversion with 2-bromo-6-methoxy phenol installed the A-ring of morphine and yielded the precursor for the second radical cyclization. Exposure of compoud **148** to radical conditions resulted in a single diastereomer **149**. Reduction of the oxazilidinone **149** with DIBAL-H, desilylation, hydrogenation and Swern oxidation furnished the ketoaldehyde **150**. Friedle-Crafts cyclization was initiated by treatment of the ketoaldehyde with trifluoromethane sulfonic acid closing the D-ring to give 10-hydroxy-14-*epi*-hydrocodone **151**. If the oxazolidinone was reduced to the alcohol and mesylated it would allow for the D-ring to be closed via displacement.

In 1998, Hudlicky disclosed his second radical cyclization approach to morphine. His synthesis started with the dioxygenase mediated dihydroxylation of β-bromoethylbenzene **154** (Scheme 17). Diimide reduction and protection of the distal alcohol gave the silyl ether **156**.



Reagents and conditions: i) *E.* coli JM109 (pTDG602) (10g/L); ii) PAD, AcOH, MeOH (80%); iii) TBSOTf, *i*-Pr_2NEt, CH_2Cl_2 (47%); iv) $PhCO_2H$, DEAD, *n*-Bu_3P, THF (84%); v) 2-oxazolidone, NaH, DMSO (71%); vi) NaOH, H_2O; vii) 2-bromo-6-methoxy phenol, DEAD, *n*-Bu_3P, THF (28% over two steps); viii) $(TMS)_3SiH$, AIBN, 140 °C, sealed tube (15%).

Scheme 17. Hudlicky's second generation radical cyclization approach.

Mitsunobu inversion of the allylic hydroxyl with benzoic acid followed by displacement of the alkyl bromide with oxazol-2(3H)-one and ester hydrolysis allowed for selective deprotection of the allylic alcohol provided the C-Ring fragment of morphine **157.**

Installation of the A ring was performed by a second Mitsunobu with 2-bromo-6-methoxy phenol to set the correct stereochemistry at C-5. Exposure of compound **158** to tris(trimethylsilyl)silane and azobisisobutyronitrile afforded a complex mixture of compounds. Column chromatography of the mixture afforded compound **160** as the predominate diastereomer in a yield of 15%. Trace amounts of a second

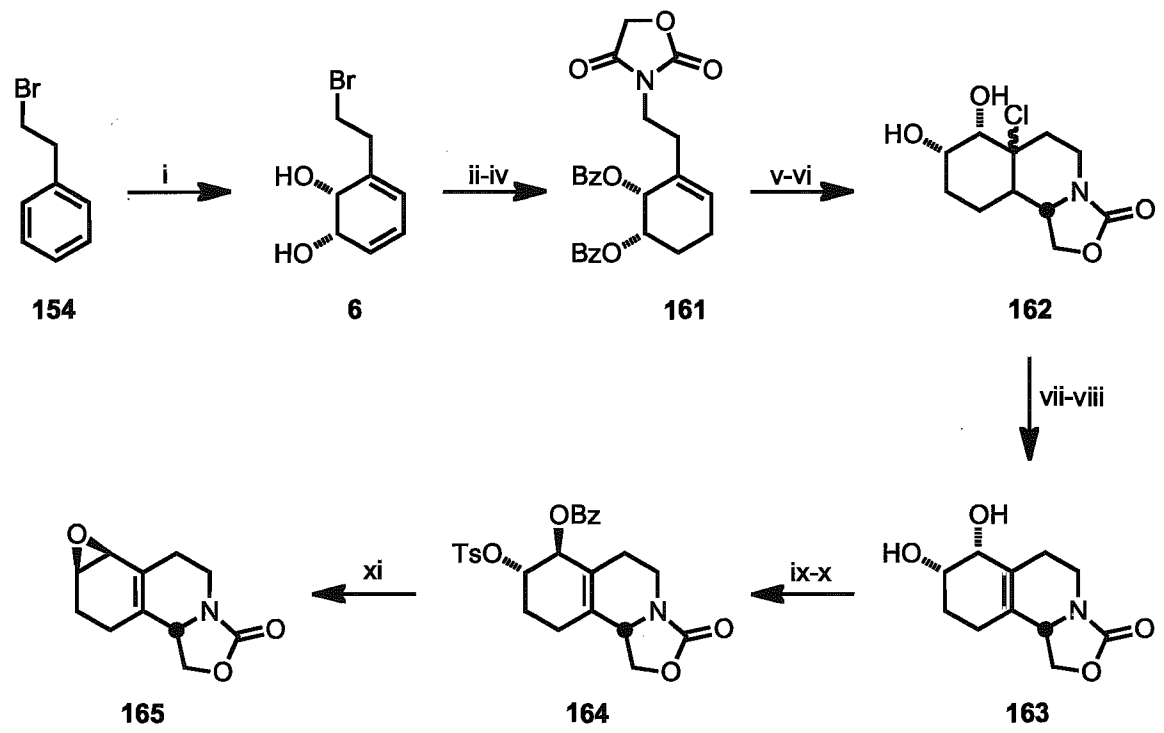
diastereomer **159** were detected. Hudlicky's previous methods to close the D-ring would finish the core of morphine.

Heck cyclization Approach[89-90, 93-95]

The Hudlicky group also explored the use of a Heck cyclization strategy to correct the C-14 stereochemistry that the radical cyclizations produced when the C9-C14 bond was inplace. Similar to the radical cyclization approaches the isoquinoline intermediate was used to install the B- and C-rings. Biooxidation of β-bromoethylbenzene **154** provided the chiral starting material **6** (Scheme **18**). The *cis*-cyclohexadienediol **6** was treated with potassium azodicarboxylate with acid to selectively reduce the distal olefin, the hydroxyl groups were esterified and the alkyl halide was displaced with oxazoldine-1,4-dione to give the heterocycle **161**.

The more reactive amide carbonyl was reduced with sodium borohydride and then treated with aluminum chloride to induce an *N*-acyliminium ion-olefin cyclization to give the iosquinoline **162**. Elimination of the alkyl chloride with 1,8-diazabicyclo[5.4.0]undec-7-ene followed by ester hydrolysis furnished diol **163**. Selective protection of the homoallylic hydroxyl group with *p*-toluenesulfonyl chloride followed by Mitsunobu inversion of the allylic hydroxyl afforded bis

protected *trans* diol **164.**

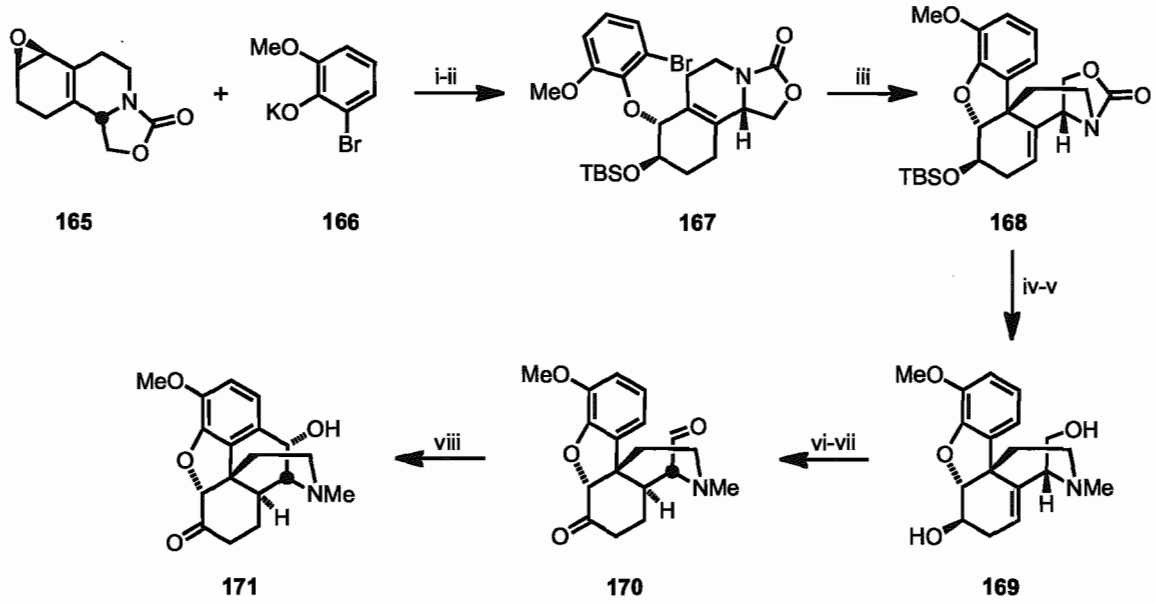


Reagents and conditions: i) *E.* coli JM109 (pTDG602) (10g/L); ii) PAD, AcOH, MeOH (80%); iii) $PhCO_2H$, DCC, CH_2Cl_2 (83%); iv) oxazoldine-1,4-dione, tetramethylguanidine, THF (77%); v) $NaBH_4$, MeOH, THF (qunat.); vi) $AlCl_3$, CH_2Cl_2 (57%, *cis*:*trans* = 3.7:1); vii) DBU, DMSO, reflux (25%); vi) LiOMe, THF (85%); vii) TsCl, pyridine, DMAP (45%); $PhCO_2H$, PPh_3, DEAD, THF (84%); k) NaOMe, MeOH, THF (65%).

Scheme 18. Synthesis of the isoquinoline derivative.

Basic ester hydrolysis of compound **164** resulted in epoxide **165.** Regio- and setereoselective opening of the epoxide **165** with the potassium salt of bromoguaicol **166** and protection of the resulting hydroxyl as the silyl ether furnished **167** (scheme 19). An intramolecular Heck reaction gave the pentacyclic carbamate **168.** Reduction and treatment with tetra-*n*-butylammonium fluoride provided alcohol **169.** Compound **169** was subjected to hydrogenation with Adam's catalyst and Swern oxidation that resulted in the unexpected epimer at C-14.

Treatment of the ketoaldehyde **170** with trifluoromethanesulfonic acid finished the synthesis of 10-hydroxy-14-*epi*-hydrocodone **171.**

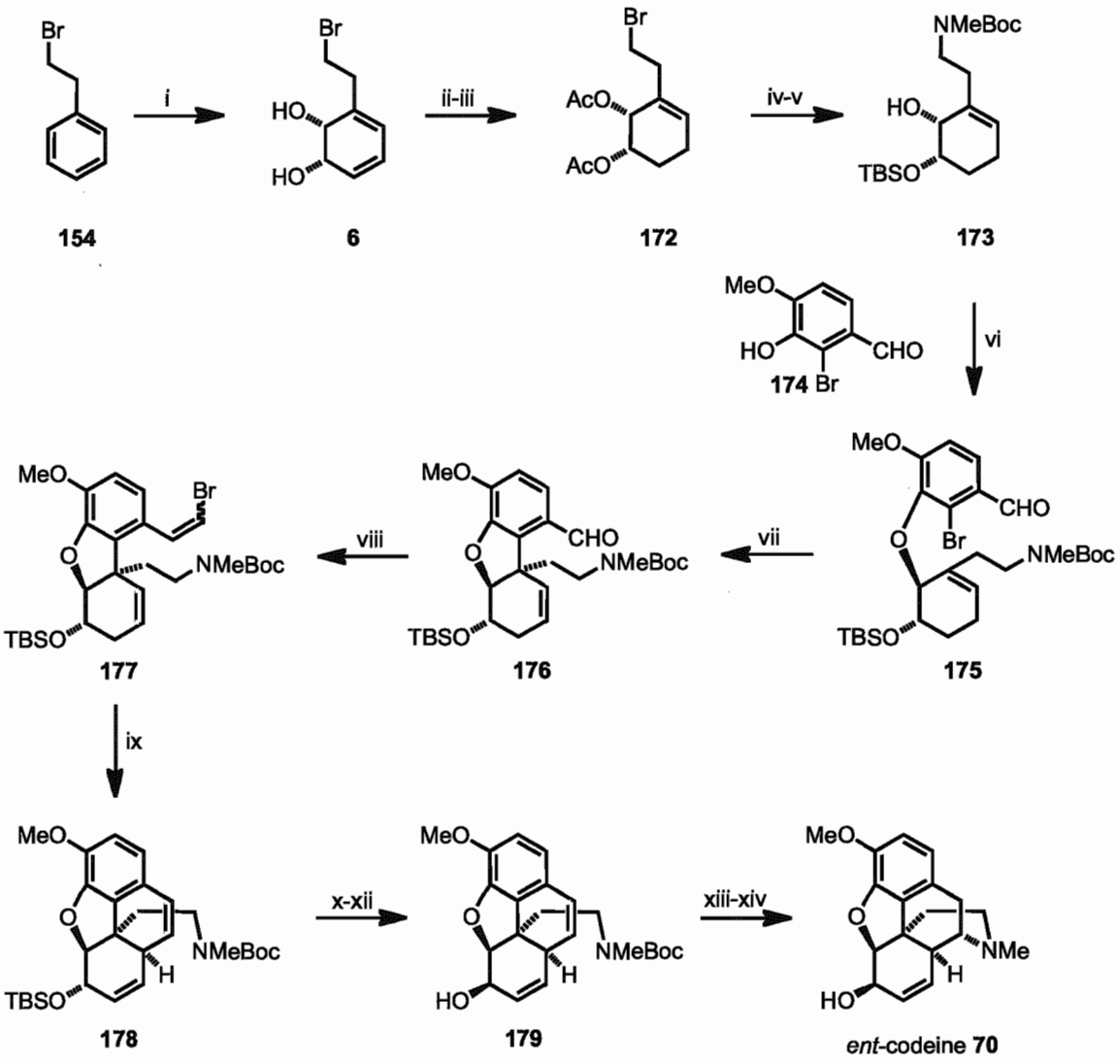


Reagents and conditions: i) DME, 18-crown-6 (80%); ii) TBSOTf, *i*Pr_2NEt, CH_2Cl_2 (74%); iii) $Pd(PPh_3)_4$, Proton Sponge™, toluene (74%); iv) DIBAL-H, CH_2Cl_2 (69%); v) TBAF, THF, H_2O (77-86%); vi) H_2, PtO_2, AcOH (64%); vii) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; viii) TFA (30% over two steps).

Scheme 19. Hudlicky's Heck cyclization approach to morphine.

In Hudlicky's second generation of his Heck cyclization approach, he employed two intramolecular Heck cyclizations to construct the C-B-D rings of morphine. This approach like the previous utilized the same *cis*-cyclohexadienediol **6** as the chiral precursor (scheme 20). The distal olefin was selectively reduced with diimide followed by protection of the hydroxyl to give the diacetate **172.** Treatment of the diacetate with methylamine gas in a sealed tube and then di-*tert*-butyl carbonate resulted in substituion of the alkyl bromide and subsequent hydrolysis of the diacetates. Selective protection of the homoallylic hydroxyl as the

silyl ether furnished the C-ring fragment **173**. Mitsunobu inversion with bromoisovanillin **174** gave the aryl bromide **175** and the first Heck reaction closed the E-ring.



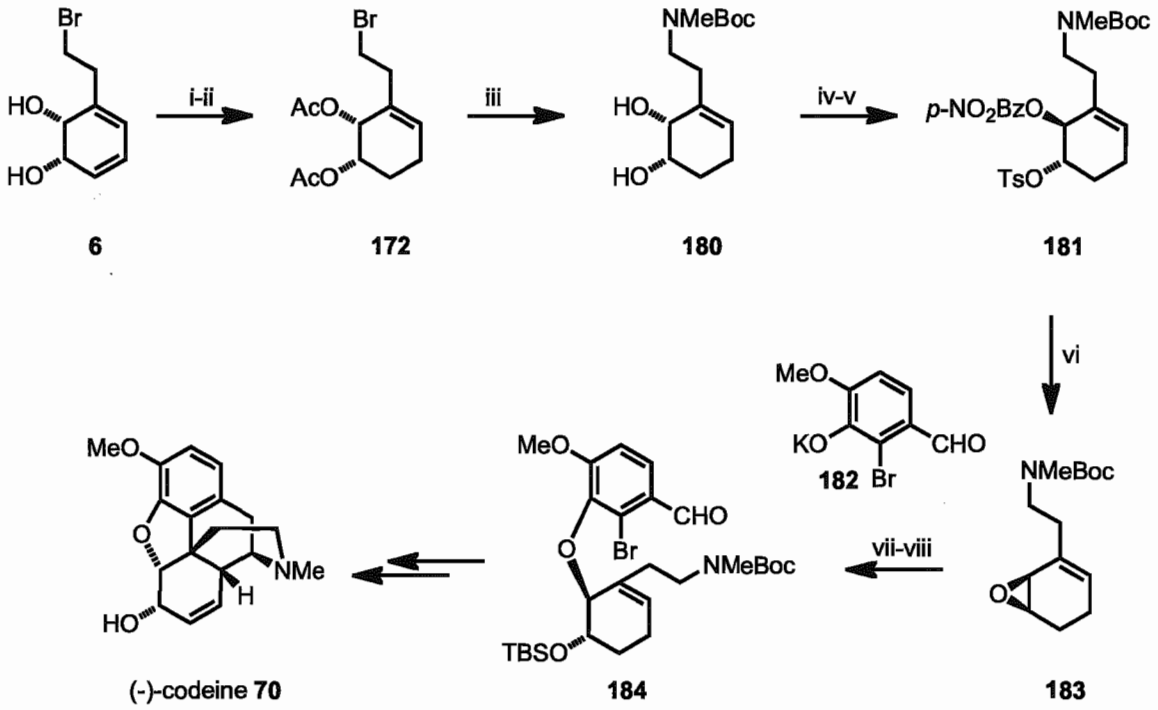
Reagents and conditions: i) *E.* coli JM109 (pTDG602) (10g/L); ii) PAD, AcOH, MeOH (80%); iii) Ac_2O, NEt_3, DMAP, CH_2Cl_2 (79%); iv) a) $MeNH_2$, K_2CO_3, THF, -40 °C to 0°C; b) $(Boc)_2O$, NEt_3, MeOH (50%); v) TBSCl, imidazole, CH_2Cl_2 (88%); vi) *n*-Bu_3P, DIAD, THF, 0°C (55%); vii) $Pd(OAc)_2$, Ag_2CO_3, dppf, toluene, 110°C (82%); viii) $PPh_3CH_2Br_2$, *t*-BuOK, THF -60°C (49%); ix) $Pd(OAc)_2$, Ag_2CO_3, dppp, toluene, 110°C (44%); x) TBAF, THF; xi) IBX, DMF; xii) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0°C (72% over three steps); xiii) TFA, CH_2Cl_2 (88%); xiv) a) $Hg(OAc)_2$, NEt_3; b) $LiALH_4$ (18%).

Scheme 20. Hudlicky' Synthesis of *ent*-codeine.

A Wittig reaction on aldehyde **176** provided the vinyl bromide **177**. The second Heck precursor **177** was subjected to the second Heck reaction completing the

phenanthrene core. Deprotection of the silyl ether **178** followed by oxidation/ reduction sequence was performed to set the correct stereochemistry at C-6 furnishing allylic alcohol **179**. Carbamate hydrolysis gave the enantiomer to Trost's intermediate.[83] Attempts to repeat Trost's conditions were unsuccessful. Therefore the olefin was subjected to oxymercuration that was quenched with the ethylamino bridge. Subsequent lithium aluminum hydride reduction completed the synthesis of *ent*-codeine **70**.

Utilizing the aforementioned approach, Hudlicky published his enantiodivergent synthesis of (+)- and (-)-codeine in 2009. This synthesis started with the same diol **6** as his 2007 publication. Selective reduction of the distal olefin with potassium azodicarboxylate, protection of the hydroxyls as the diacetates yielded **172**. Subjecting diacetate **172** to methylamine gas in a sealed tube and subsequent protection with *tert*-butyl carbamate provided diol **180** (scheme 21).



Reagents and conditions: i) *E.* coli JM109 (pTDG602) (10g/L); ii) PAD, AcOH, MeOH (80%); iii) Ac_2O, NEt_3, DMAP, CH_2Cl_2 (79%); iv) a) $MeNH_2$, K_2CO_3, THF, -40 °C to 0°C; b) $(Boc)_2O$, NEt_3, MeOH (50%); v) *p*-$NO_2C_6H_4CO_2H$, DIAD, PPh_3, THF (71%); v) TsCl, NEt_3, DMAP, CH_2Cl_2 (73%); vi) NaOMe, MeOH, THF (88%); vii) **5**, 18-crown-6, DME-DMF (75%); viii) TBSCl, imidazole, CH_2Cl_2 (61%).

Scheme 21. Hudlicky's synthesis of of (-)-codeine.

Following a procedure developed by Banwell,[28] the allylic alcohol was inverted with *p*-nitrobenzoic acid via Mitsunobu inverion. Protection of the homoallylic hydroxyl with *p*-toluenesulfonyl chloride gave the tosylate **181**. Basic ester hydrolysis allowed for the displacement of the tosylate furnished the epoxide **183**. Selective opening of the epoxide with the potassium salt of bromoisovanillin **182** and subsequent silyl protection gave the enantiomer **184**. This can be converted following Hudlicky's previously reported protocols to give the natural isomer of codeine **70**.

3. Discussion

3.1 Introduction

Morphine, codeine and other semi-synthetic opiods are among the most commonly used pharmaceuticals. The consumption of morphine in North America for 2011 is estimated to be approximately 106 tonnes[31]. The supply of opium alkaloids depends solely on the isolation from the opium poppy. Which can only be harvested from opium plants grown in a few specific regions, including Iran, Afghanistan, Turkey and India. Many of these countries are under political turmoil, making the supply of opiates questionable. In order to relieve the Western world's reliance on these countries a practical synthesis that rivals that of isolation from the opium poppy is required. Despite the numerous syntheses of morphine and its congeners, not one is practical enough to be a viable supply for the world's demands. One of the long standing goals of the Hudlicky group is the development of an efficient, economically viable and environmentally benign synthetic route to opium alkaloids. Professor Hudlicky's approach to the synthesis of opiates is unique as the chiral starting material is obtained from the enzymatic dihydroxylation of arenes. The present thesis discusses the synthesis of *ent*-neopinone. All strategies discussed begin with the toluene dioxygenase dihydroxylation of β-bromoethylbenzene providing sufficient quantities of enantiomerically pure *cis*-cyclohexadienediol **6** (Figure 13).

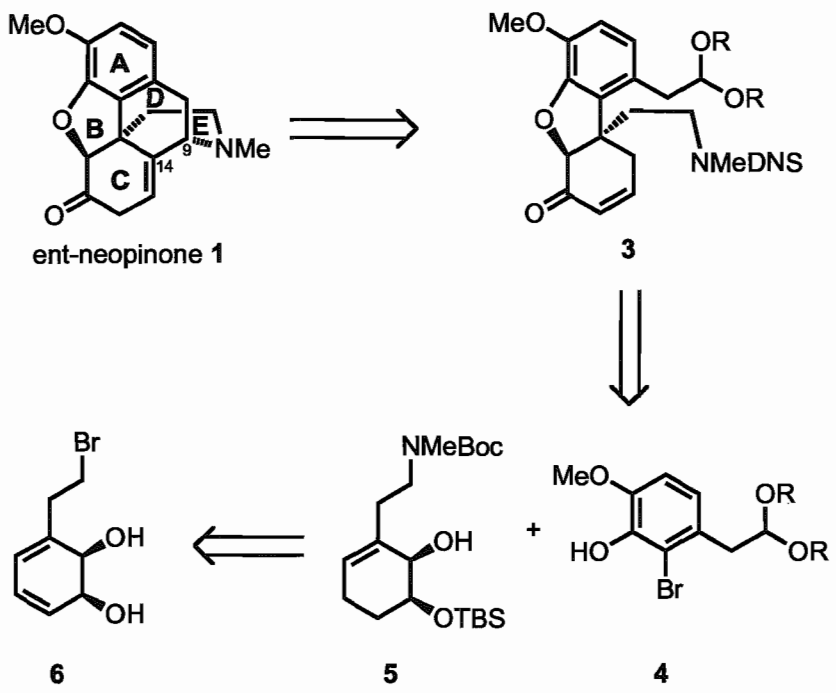


Figure 13. Retrosynthetic analysis.

A Mitsunobu inversion of allylic alcohol **5** with an appropriate arene **4** can be used to fasten the A ring to the C ring via the ether linkage. Closure B ring can be accomplished by an intramolecular Heck reaction thus giving advanced intermediate **3**. It was envisioned there were three distinct routes to close the D and E rings to furnish the pentacyclic core of neopinone (figure 14).

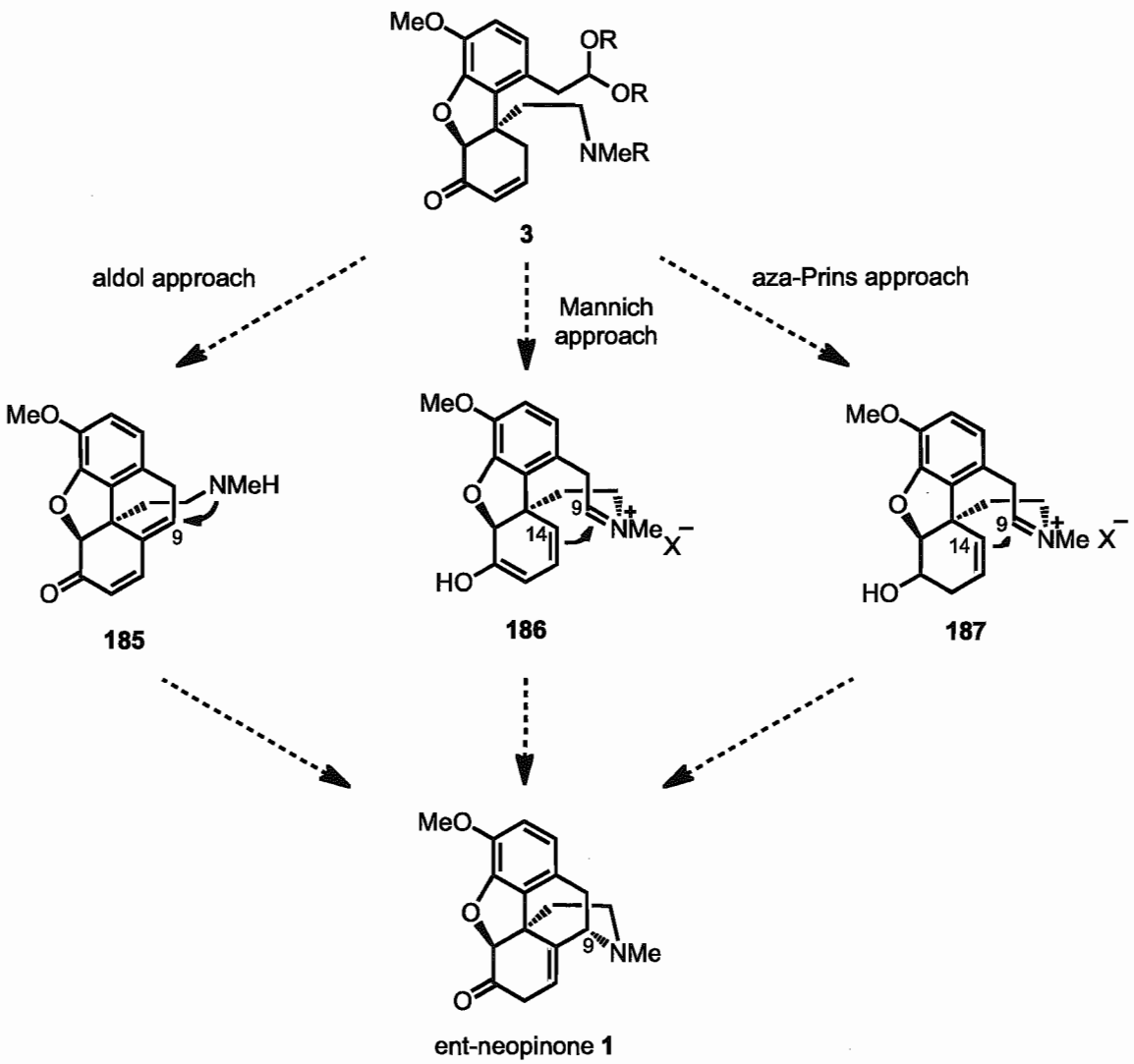
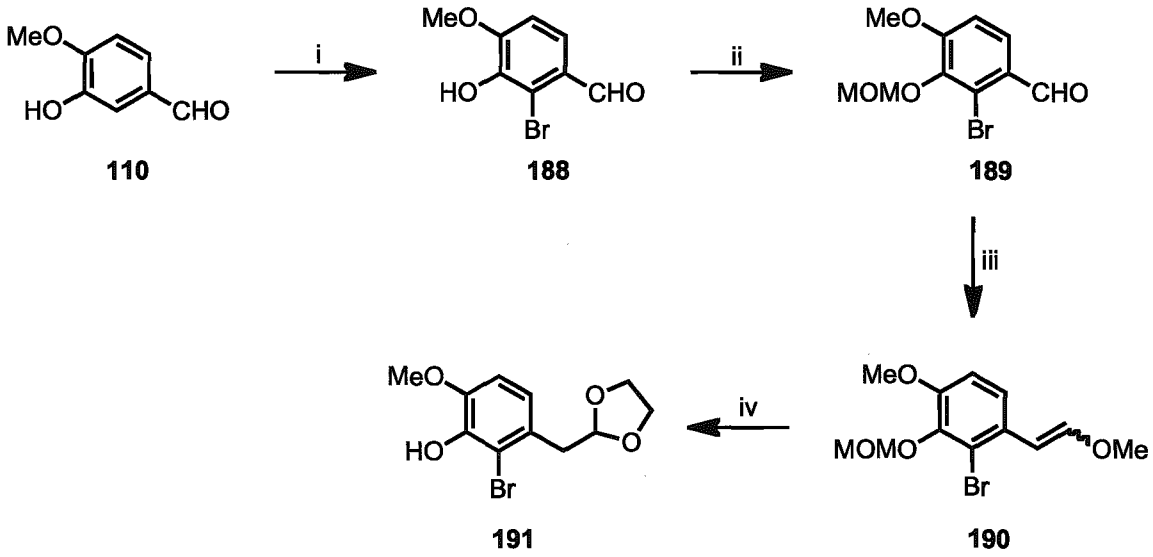


Figure 14. Closure of the D and E ring of neopinone.

The first approach is a composed of an aldol closure where upon condensation of the aldehyde and C-ring enone, the ethylamino bridge would add 1,6 at C-9. The second approach consists of closure of the C-9 and C-14 bond by an aza-Prins reaction on the iminium species **187**. Equally, the third approach would under go a γ-Mannich clousure on the iminium salt **186**. These approaches and the conclusion of our chemoenzymatic synthesis of *ent*-neopinone is discussed herein.

3.2 Synthesis of A-ring

The A-ring synthesis starts from isovanillin **110,** which was brominated using *N*-bromosuccinimde to provide bromoisovanillin **188**. Protection of the phenol as the MOM ether and subsequent wittig elongation using the ylide generated from (methoxymethyl)triphenylphosphonium chloride furnished the (*E*)- and (*Z*)-enol ethers **190**. The (*E*)- and (*Z*)-enol ethers were exposed to ethylene glycol under acidic conditions to give the A-ring fragment **191** in an overall yield of 48%.



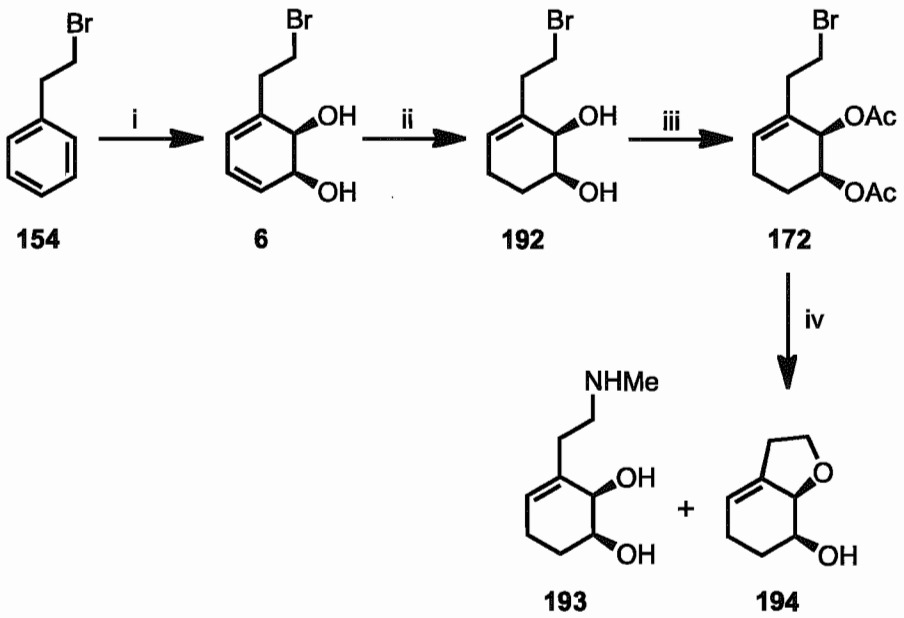
Reagents and conditions: i) NBS, $CHCl_3$, reflux (68%); ii) MOMCl, *i*Pr_2NEt, CH_2Cl_2, 4 °C; (iii) $ClPh_3PCH_2OCH_3$, *t*BuLi, THF, –78 °C to 4 °C; (iv) $(CH_2OH)_2$, *p*TsOH, THF, reflux (76% over three steps).

Scheme 23. Synthesis of the A-Ring fragment.

3.3 Synthesis of C-ring

Following the previously reported Hudlicky approach to the desired Boc carbamate **5**,[93] the synthesis started with the microbial oxidation of β-

bromoethylbenzene **154** using *E. coli* JM109 (pTDG601A)[11] furnishing the *cis*-cyclohexadiene diol **6** in 10 g per liter of cell broth (scheme 24). Dimide reduction of the distal olefin using potassium azodicarboxylate and acetic acid afforded the allylic alcohol **192** in 83% yield. Protection of the diol moiety with acetic anhydride and triethylamine provided the bisacetate **172**. However in our hands, following the previously published protocol, treatment of compound **172** with methylamine and potassium carbonate, provided the desired amine **193** in low yields with a major contaminate being furan **194**.

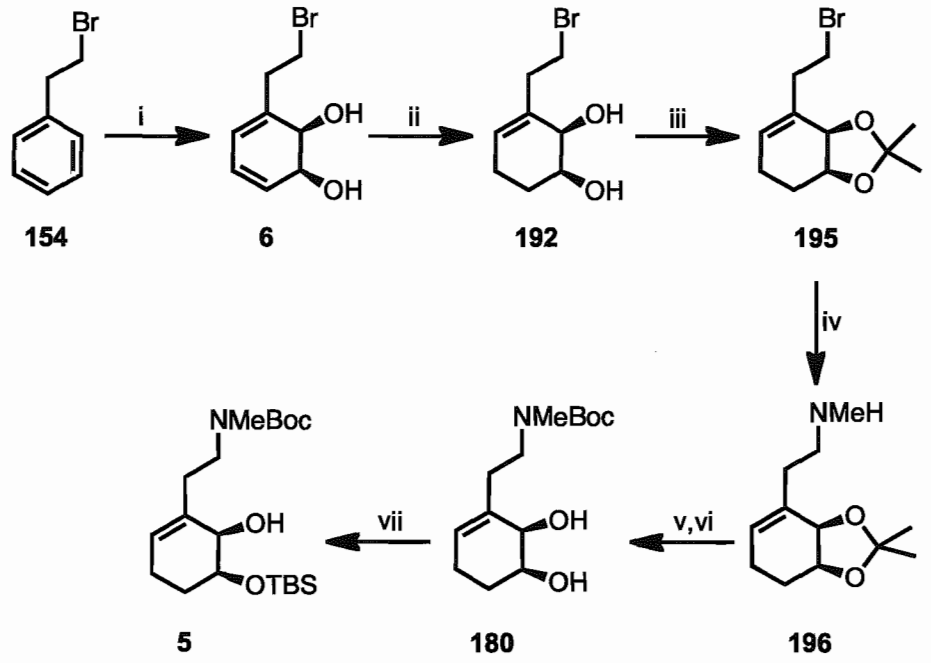


Reagents and conditions: i) *E.* coli JM109 (pTDG602) (10g/L); ii) PAD, AcOH, MeOH (80%); iii) Ac_2O, NEt_3, DMAP, CH_2Cl_2 (79%); iv) $MeNH_2$, K_2CO_3, THF, -40 °C to 0°C.

Scheme 24. Preparation of C-ring

The obvious solution to this problem was the utilization of an alternative protecting group. We chose to protect the diol as its acetonide preventing any achnce of furan formation. Treating intermediate **192** with 2,2-diemthoxypropane

and catalytic *p*-toluenesulfonic acid generated the acetonide **195** in 80% yield. Following the same amination protocol as before acetonide **195** was smoothly converted to methyl amine **196** in 90% yields with no contamination by the furan. A one pot hydrolysis of the acetonide followed by protection of the amine provided carbamate **180**. Regioselective protection of the distal hydroxyl gave the C-ring fragment **5** in 31% overall yield. This optimized route allowed for multigram scale synthesis of the C-ring fragment.

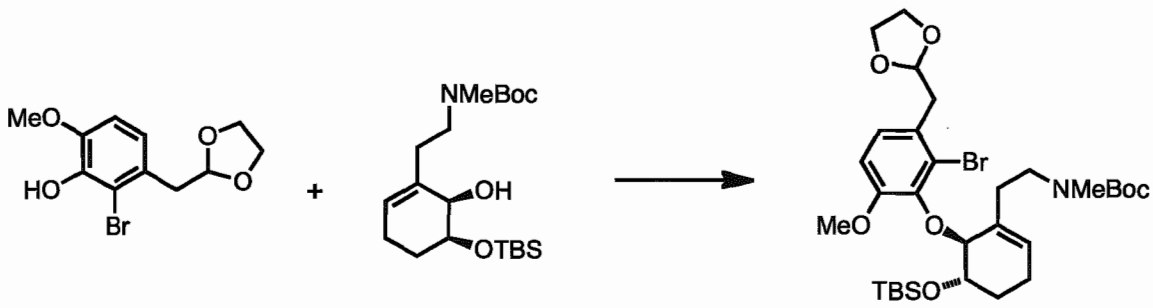


Reagents and conditions: i) *E.* coli JM109 (pTDG602) (10g/L); ii) PAD, AcOH, MeOH (80%); iii) 2,2-dimethoxypropane, acetone, *p*TsOH (80%); iv) $MeNH_2$, K_2CO_3, THF, sealed tube (90%); v) 3N HCl, EtOH; vi) Boc_2O, $NaHCO_3$, EtOH (72% over two steps); vii) TBSCl, imidazole, CH_2Cl_2, -78 °C to 25 °C (80-88%).

Scheme 25. Revised route to C-Ring fragment **5**.

3.4 Generation of the key advanced intermediate

To couple the A ring fragment **191** and C ring fragment **5** a Mitsunobu reaction was envisoned. Exhaustive screening of Mitsunobu conditions (Table 1) were performed on the A and C ring fragments.



191 **5** **197**

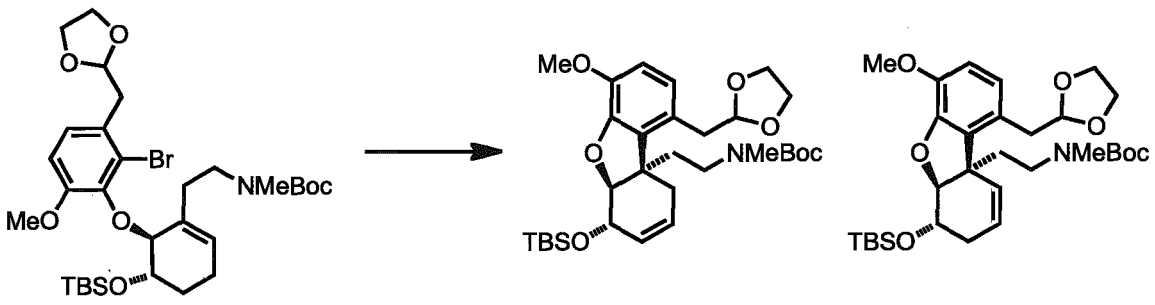
Figure 15. Mitsunobu coupling of A-ring and C-ring fragments.

Table 1. Mitsunobu coupling of A-ring and C-ring fragments.

Entry	*Azodicarboxylate*	*Solvent*	*Base*	*Temperature*	*Result*
1	DIAD	Toluene	-	RT	Trace
2	DIAD	CH_2Cl_2	-	RT	SM
3	DIAD	Et_2O	-	RT	SM
4	DIAD	THF	-	RT	44%
5	DIAD	CH_3CN	-	RT	SM
6	DIAD	THF	NEt_3	RT	35%
7	DIAD	THF	*N*-methylpiperidine		35%
8	ADDP	THF	-		29%
9	**DIAD**	**THF**	-	**-10 °C - RT**	**76%**

The use of diispropyl azodicarboxylate and tri-*n*-butyl phosphine (Table 1, entry 9) with careful control of the temperature during addition was found the give the best yield and was scaled upto multigram scale (10 g).

With the A-ring and C-ring tethered together we investigated conditions necessary for the intramolecular Heck reaction. After exhaustive screening it was found that the use of tri-*tert*-butylphospine was abosuletely required (table 2, entries 13-17) for the intramolecular Heck reaction. The palladium catalyst was found not to play as important of a role, however the use of Tris(dibenzylideneacetone)dipalladium(0) (table 2, entry 16) did result in the highest yield of 87%. Interestingly under these conditions an inseparable mixture of allylic and homoallylic silyl ethers **198** and **199** were obtained in a 1:5 ratio. The allylic TBS ether is assumed to be from the palladium-mediated isomerization of the olefin **199** to **198.**



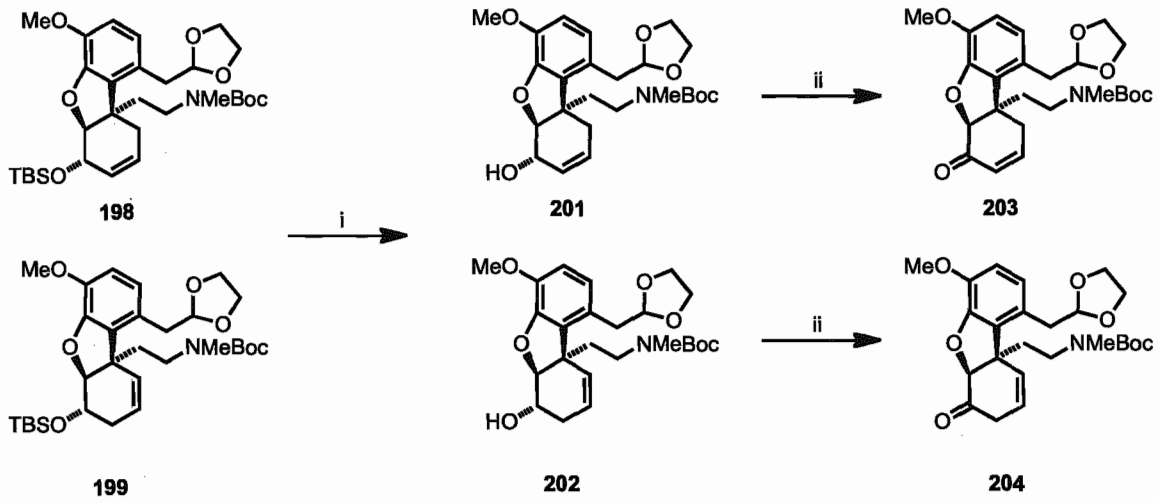
197 198 199

Figure 16. Intramolecular Heck reaction of ether **197**.

Table 2. Intramolecular Heck reaction of ether **197**.

Entry	*Phosphine*	*Palladium*	*Base*	*Additive*	*Result*
1	(*p*-tolyl)$_3$P	$Pd_2(dba)_3$	Ag_2CO_3	-	SM
2	(*p*-tolyl)$_3$P	$Pd_2(dba)_3$	NEt_3	-	SM
3	(*o*-furyl)$_3$P	$Pd(OAc)_2$	Ag_2CO_3	-	SM
4	(*o*-furyl)$_3$P	$Pd(OAc)_2$	NEt_3	-	SM
5	DPPE	$Pd(OAc)_2$	Ag_2CO_3	-	SM
6	DPPE	$Pd(OAc)_2$	NEt_3	AgOTf	SM
7	(*o*-furyl)$_3$P	$Pd(OAc)_2$	Cs_2CO_3	$NiBr_2$/NaI	decomposition
8	(*o*-furyl)$_3$P	$Pd(OAc)_2$	NEt_3	$NiBr_2$/NaI	decomposition
9	DPPF	$Pd(OAc)_2$	Cs_2CO_3	$NiBr_2$/NaI	decomposition
10	DPPF	$Pd(OAc)_2$	NEt_3	$NiBr_2$/NaI	decomposition
11	DPPF	$Pd(OAc)_2$	Ag_2CO_3	$Tl(OAc)_2$	SM
12	*t*Bu$_3$P	$Pd(OAc)_2$	MeDCHA	-	19%
13	***t*Bu$_3$P**	**$Pd(OAc)_2$**	**Cs_2CO_3**	-	**74%**
14	*t*Bu$_3$P	$Pd_2(dba)_3$	MeDCHA	-	60%
15	*t*Bu$_3$P	$Pd_2(dba)_3$	Cs_2CO_3	-	full conversion
16	***t*Bu$_3$P**	**$Pd_2(dba)_3$**	**K_2CO_3**	-	**87%**
17	***t*Bu$_3$P**	**$Pd(OAc)_2$**	**K_2CO_3**	-	**73%**

Treatment of silyl ether **198** and **199** with tetra-*n*-butylammonium fluoride furnished the allylic and homoallylic alcohols **201** and **202** respectively. After the silyl deprotection the isomers where easily separable by column chromatography. Oxidation using IBX provided us with access to the key intermediate **204** and its isomer **203**.



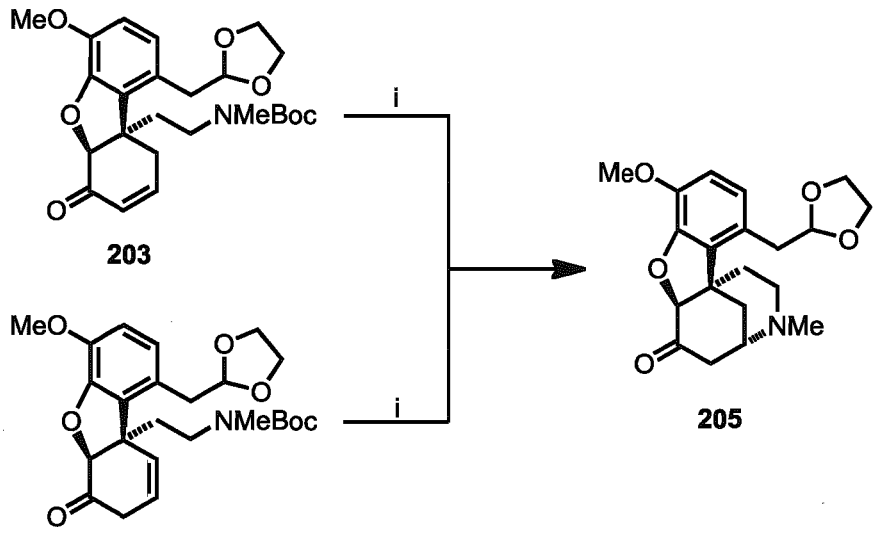
Reagents and conditions: i) TBAF, THF, -78 °C – RT (83-85%); ii) IBX, EtOAc, reflux.

Scheme 26. Perparation of advanced intermediates **203** and **204.**

Column chromatography of these enones, using either neutralized silica gel or alumnia, proved to be poor, resulting in low isolated yields, despite their relative purity of the crude product by TLC and ^{1}H NMR. Therefore these were used crude for subsequent reactions.

3.5 Attempts to Close B and D ring

With the advanced intermediates **203** and **204** in hand we set out to investigate the various proposed closures of the B and D rings. Treatment of **203** and **204** with trifluoroacetic acid cleanly gave the [3.3.1] bicyclic compound **205**, with out any of the expected condensation of the secondary amine with the masked aldehyde (scheme 28).

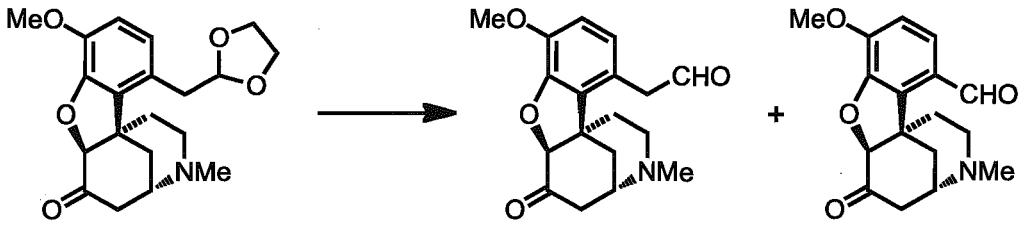


Reagents and conditions: i) TFA, CH_2Cl_2 (44-55% over two steps).

Scheme 28. Formation of bicyclic adduct **205**.

Despite no evidence for formation of the condensed iminium species **186**, we hoped that after hydrolysis of the acetal we could force an equilibrium towards the desired iminium species **186** by using either basic or acidic conditions.

With this in mind we screened numerous conditions for the hydrolysis of the acetal as seen in Table 3. Ultimately the best result for the hydrolysis was found when using oxalic acid in water at 40 °C affording the desired aldehyde **206** in 88-92% yields.



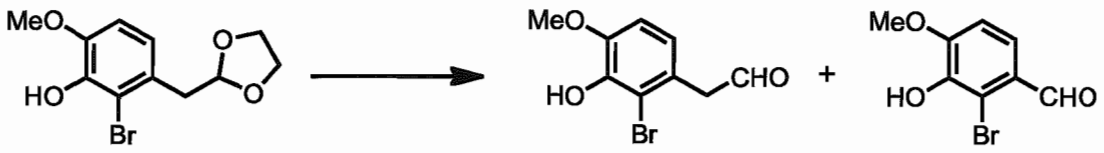
205 **206** **207**

Figure 17. Hydrolysis of acetal **205**.

Table 3. Hydrolysis of acetal **205**.

Entry	*Reagents*	*Solvent*	*Temp*	*Result*
1	HCl	MeCN/MeOH	45 °C	**206** + **207** (30%)
2	$SnCl_4$	CH_2Cl_2	RT	**206** (<10%)
3	$CeCl_3 \bullet 7H_2O$, NaI	MeCN	RT	SM
4	$PdCl_2$	acetone	RT → 55 °C	SM
5	*p*PTs	H_2O, acetone	RT → 55 °C	SM
6	*p*TsOH	3-pentanone	RT → 55 °C	SM
7	CAN	MeCN, H_2O	RT → 55 °C	SM
8	$(CO_2H)_2$	H_2O	RT	**206** (trace)
9	**$(CO_2H)_2$**	**H_2O**	**40 °C**	**207 (88-92%)**

It is interesting to note that when treating the acetal with hydrochloric acid in acetonitrile and water it afforded a mixture of two aldehydes **206** and **207** in various ratios depending on the reaction time. When the homoaldehyde **206** was treated under the same conditions it cleanly converted to **207**. Out of curiosity we investigated what was causing the presence of the "cleaved" aldehyde by screening various reaction conditions (Figure 18).



191 **208** **209**

Figure 18. Generation of byproducts from the hydrolysis of acetal **208**.

Table 4. Generation of byproducts from the hydrolysis of acetal **5**.

Entry	*Reagent*	*Solvent*	*Temperature*	*Result* (**208**:**209**)
1	$(CO_2H)_2$	H_2O	40 °C	75:25
2	HCl	MeCN, H_2O	40 °C	22:78
3	HCl	MeCN, H_2O, degassed	40 °C	95:5

Treatment of the phenol **191** with aquesous oxalic acid at 40 °C afforded a mixture of homobenzaldehyde **208** and benzaldehyde **209** in a 3:1 ratio. Where as the reaction in aqueous acetonitrile with hydrochloric acid gave the benzaldehyde **209** as the major product. When treated with degassed hydrochloric acid and aqueous acetonitrile at 40 °C the major product was primarily the homobenzaldehyde **208**. Aside from the apparent solvent effects it is obvious that oxygen played a critical role in cleavage of the homobenzaldehyde. The proposed mechanism for the formation of benzaldehyde **207** is shown in Figure 19. The presence of oxygen in the transformation likely involves an oxidation of the benzylic position leading to intermediate **210**, which is then converted, via **211**, to hydroperoxide **212**. Fragmentation of **213** then leads to benzaldehyde **207** and formic acid.

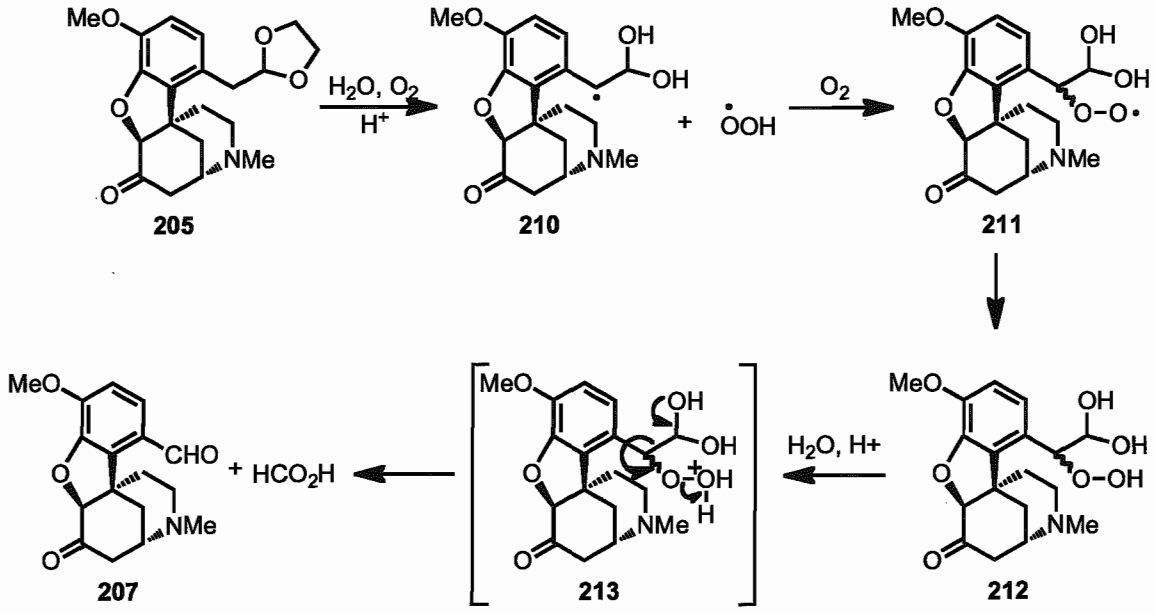


Figure 19. Proposed mechanism for the formation of benzaldehyde 207.[96]

With aldehyde **206** in hand we attempted to we attempted to force an equilibrium towards the desired iminium species **186** in we could close the C9 and C14 bond via a mannich reaction. We anticipated screening various acidic or basic conditions could invoke the retro-addition necessary to create the desired iminium species **186**. However, all conditions screened (Table 5) failed to return any thing but the bicyclic precursor **206**. It appeared after screening numerous conditions the 1,4 adduct was a thermodynamic pit preventing iminium formation and any chance to close the C9-C14 bond.

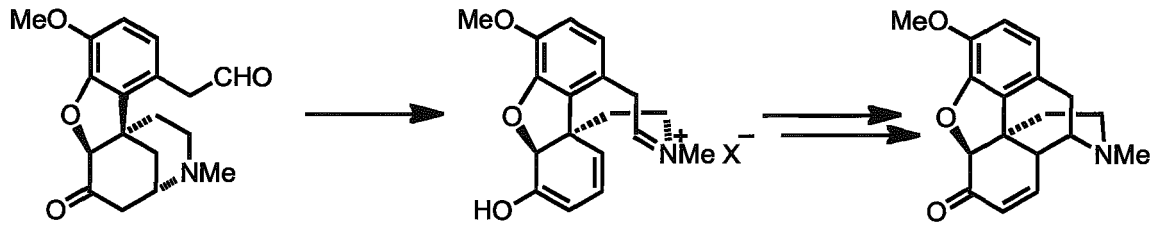
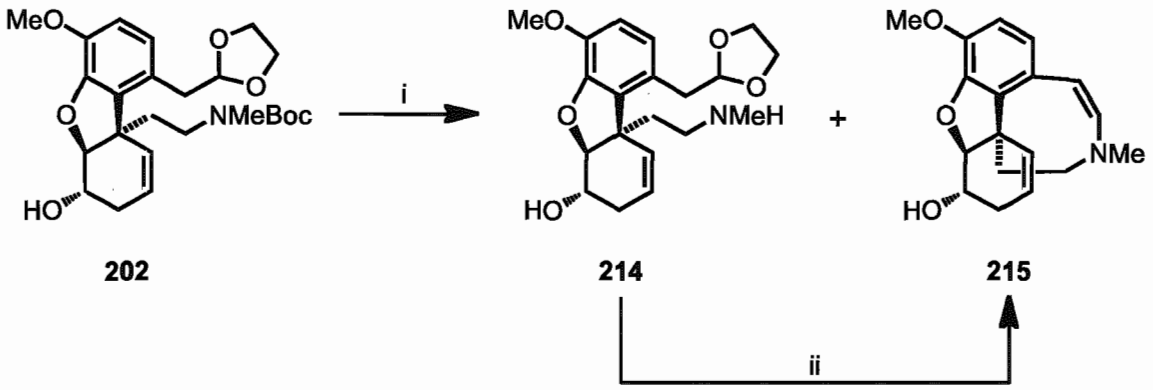


Figure 20. Attempts to close the C9-C14 bond via Mannich reaction.

Table 5. Attempts to close the C9-C14 bond via Mannich reaction.

Entry	*Reagents*	*Solvent*	*Temp*	*Result*
1	10% H_3PO_4	H_2O	RT - 45 °C	SM
2	80% AcOH	H_2O	RT - 45 °C	SM
3	AcCl	MeOH	0 °C - RT	SM
4	HCl	Et_2O	0 °C - RT	SM
5	TMS-Cl, *t*BuOK	THF	0 °C - 45 °C	SM
6	AcOH/NaOH pH4	H_2O	RT	SM
7	AcOH/NaOH pH5	H_2O	RT	SM
8	AcOH/NaOH pH6	H_2O	RT	SM
9	AcOH/NaOH pH7	H_2O	RT	SM
10	AcOH/NaOH pH8	H_2O	RT	SM

Without the formation of the iminium speices necessary for the Mannich reaction, we then turned our attention to aza-Prins approach to close the C9-C14 bond. Starting with the homo allylic alcohol **202** and treating it with trifluoroacetic acid in dichloromethane resulted in the formation of two products, the secondary amine **214** and the enamine **215** in a 3:1 ratio respectively (scheme 29).

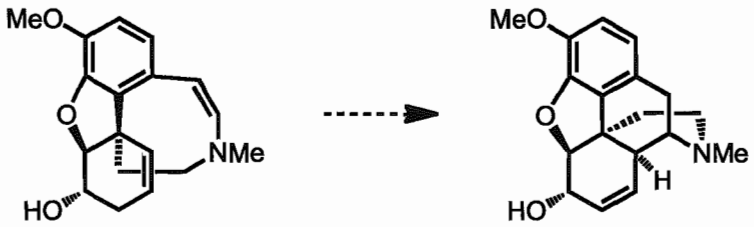


202 214 215

Reagents and conditions: i) TFA, CH_2Cl_2 (49 - 65% of **214**, 10 – 21% of **215**); ii) $(CO_2H)_2$, H_2O, 40 °C (88%).

Scheme 29. Preparation of key intermediate for aza-Prins approach.

Treating amine **214** with oxalic acid and water at 40 °C allowed for clean conversion to enamine **215**. We then treated the aza-Prins precursor **215** with various Brønsted and Lewis acids in hopes to furnish the cyclized product (Table 6).



211 212

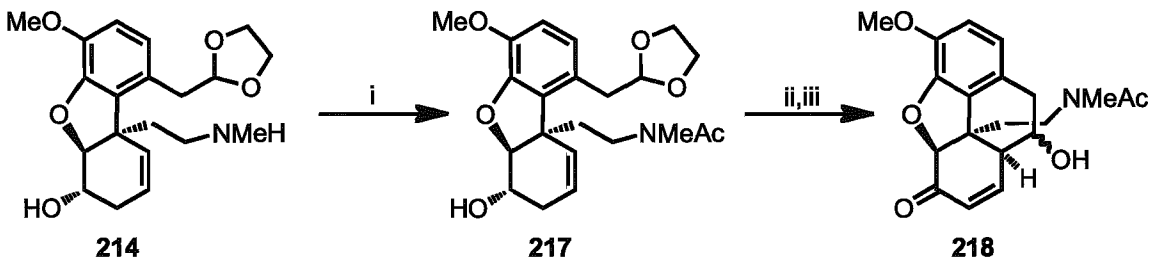
Figure 21. Investigation of the aza-Prins closure of the C9-C14 bond.

Table 6. Investigation of the aza-Prins closure of the C9-C14 bond.

Entry	*Reagent*	*Solvent*	*Temperature*	*Result*
1	$Sc(OTf)_3$	$CHCD_3$	RT	SM
2	SiO_2	-	100 °C	SM
3	85% H_3PO_4	-	RT – 40 °C	SM
4	$SnCl_4$	CH_2Cl_2	RT	SM
5	$SnCl_4$	toluene	RT - 80 °C	SM
6	AcOH	-	RT	Decomposition
7	TMSOTf	CH_2Cl_2	0 °C - RT	SM

All attempts resulted in the recovery of starting material or decomposition. Analysis by TLC or HPLC showed no compounds matching that of prepared standards. These results are similar to Fukuyama's results,[97] who envisioned a similar intermediate **186** upon which molecular modeling studies suggested that the dienone and the iminimum cation of the intermediate **187** were situated orthogonally to each other.[97] Therefore inhibiting the formation of the C9-C14 bond.

We finally turned our attention to the aldol approach to close the morphine skeleton. To test feasibility of the proposed dienone intermediate **185,** we exchanged the Boc group for the more robust acetyl group (Scheme 30).



214 **217** **218**

Reagents and conditions: i) a) AcCl, Et_3N, CH_2Cl_2, (b) MeONa, MeOH (87%); (ii) IBX, AcOEt, 80 °C; iii) 50% aqueous TFA, toluene, 50 °C (22% from **217**).

Scheme 30. Testing the feasibility of aldol approach.

Acelyation of the secondary amine **214** gave amide **217**. Oxidation of the amide **217** followed by subsequent hydrolysis of the acetal furnished a mixture of diastereomeric alcohols **218.** Isolation of the alcohols **218** affirmed the aldol approach as theses alcohols could be converted to the dienone.

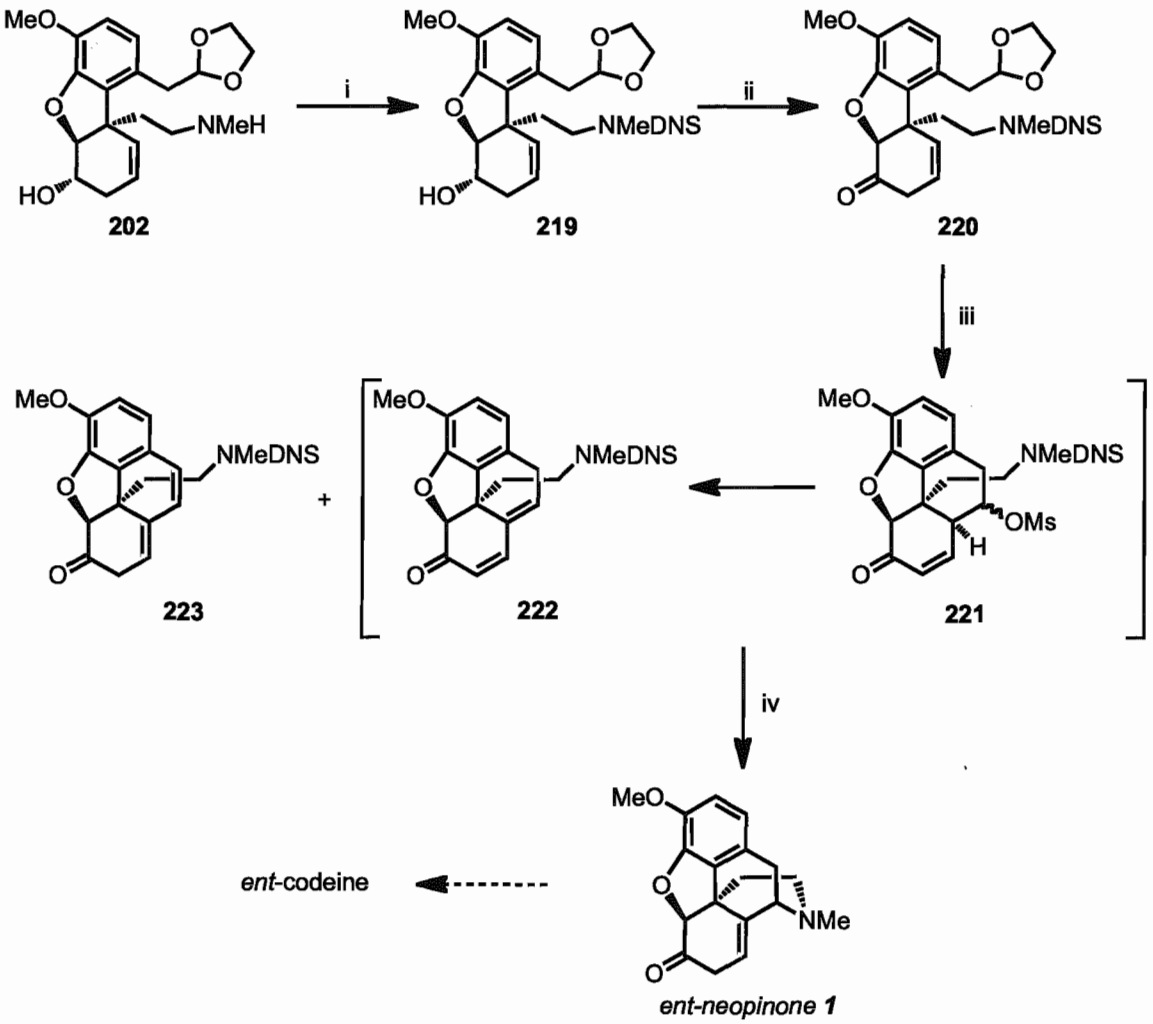
3.6 Synthesis of Neopinone

As our work was nearing completion, Fukuyama[97] reported a conceptually identical approach to the natural enantiomer of morphine. In his approach he chose to protect the amine as the 2,4-dinitrobenzenesulfonyl amide. At this point we chose to formalize our synthesis and set out to intercept Fukuyama's intermediate, as shown in scheme 31.

Taking the secondary amine **202** and treating it with 2,4-dinitrobenzenesulfonyl chloride and Hünig's base and subsequent oxidation with IBX provided us with the sulfonylamide **219**. Subjecting intermediate **220** to Fukuyama's sequence of treatment with trifluoroacetic acid in toluene followed by mesylation afforded the desired mesylate **221**. The robust nature of the cyclic acetal required longer reaction times to furnish the desired aldol intermediate product. Following Fukuyama's conditions we used 1.2 equivalents of methanesulfonyl chloride and 1.5 equivalents of Hünig's base after the intramolecular aldol leading to isolation of the mesylate **221** in only 6% yield from **219**. It is expected that traces of ethylene glycol in the reaction mixture are contributed to the low yields.

When the mesylation was performed using excess of both methanesulfonyl chloride (4.5 equivalents) and Hünig's base (5 equivalents) it led to the in *situ* elimination of the mesylate forming a mixture of **222** and **223** in a more respectable yield of 42% and 13% respectively, over two steps from **219**. The desired enone **222** was treated with thiogycolic acid in the presence of triethylamine to furnish *ent*-neopinone **1**. ^{1}H NMR and TLC analysis of the reaction mixture confirmed the

presence of neopinone **1** matching an authentic sample prepared from thebaine **69** according to Rapoport's procedure.[98]

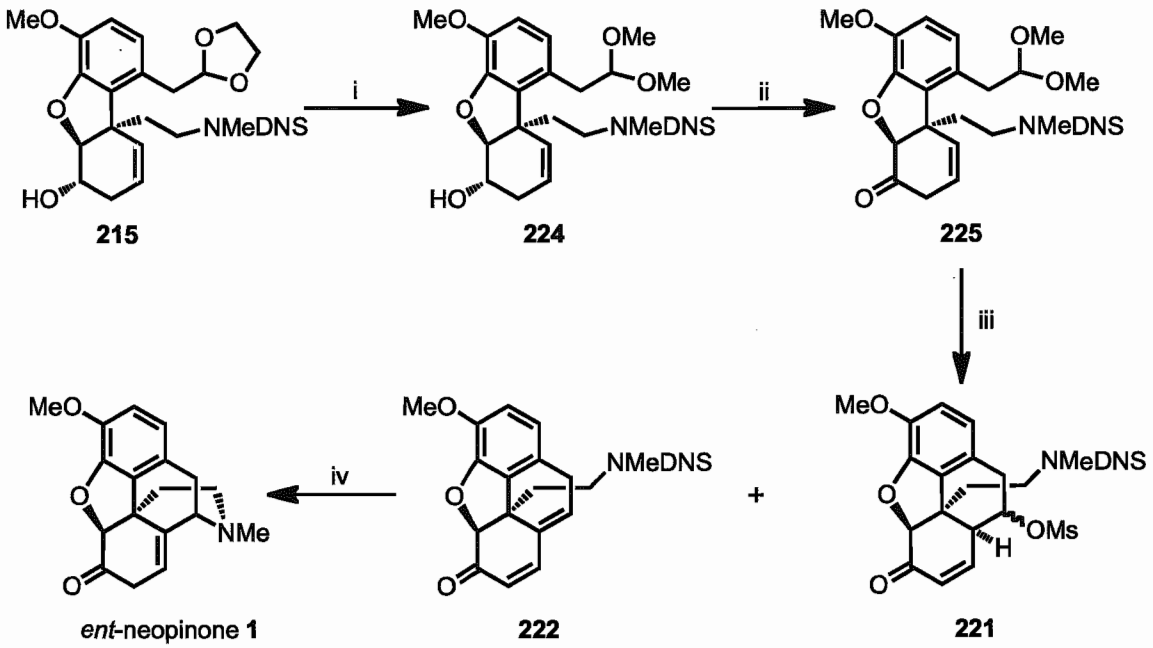


Reagents and conditions: i) 2,4-dinitrobenzenesulfonyl chloride, *i*Pr$_2$NEt, CH_2Cl_2 (51%); (ii) IBX, AcOEt, 80 °C; (iii) (a) 50% aqueous TFA, toluene, 50 °C (b) MsCl (4.5 equiv), *i*Pr$_2$NEt (5 equiv), CH_2Cl_2, 0 °C (42% of **222** from **219**, 13% of **223** from **219**); (iv) thioglycolic acid, *i*Pr$_2$NEt, CH_2Cl_2, 0 °C.

Scheme 31. Conclusion of the formal sytnthesis of *ent*-neopinone.

To guarantee that the low yields obtained from the cyclic acetal **219** were caused by the robust nature of the cyclic acetal, we chose to repeat Fukuyama's sequence with

the dimethyl acetal (scheme 32). Treatment of **215** with *p*-toluenesulfonic acid in anhydrous methanol at reflux afforded the dimethyl acetal **224**.



Reagents and conditions: i) MeOH, *p*TsOH, reflux (86%) (ii) IBX, AcOEt, 80 °C; (iii) (a) 50% aqueous TFA, toluene, 50 °C (b) MsCl (4.5 equiv), iPr_2NEt (5 equiv), CH_2Cl_2, 0 °C (24% of **221** from **224**, 28% of **222** from **224**); (iv) thioglycolic acid, iPr_2NEt, CH_2Cl_2, 0 °C.

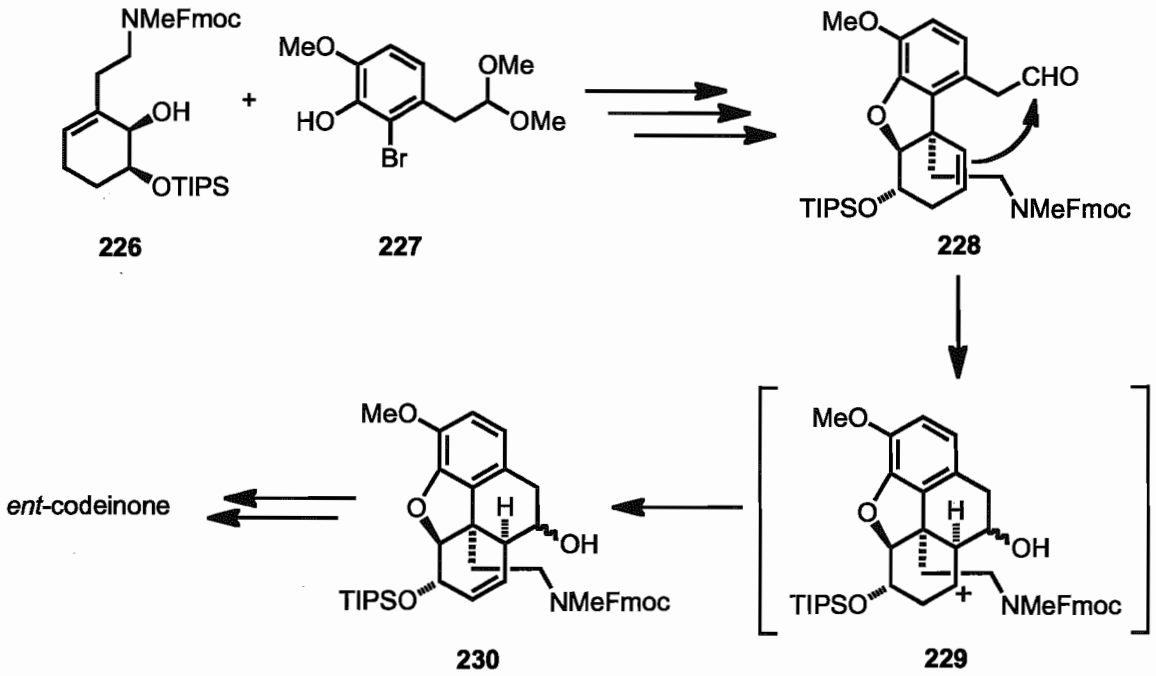
Scheme 32. Reproduction of Fukuyama's sequence to morphine.

Oxdiation of **224** with IBX furnished ketone **225** with an optical rotation of +25.5° opposite to that of the natural isomer (-24.2°).[97] Treating ketone **225** with trfluoroacetic acid followed by mesylation provided the mesylate **221** in 28% yield and dienone **222** in 24% yield from **224**. This confirmed our suspicion that the robust protecting group was the reason for the lower yields. Treatment of the mixture of **221** and **222** with thioglycolic acid and Hünig's base, as reported by Fukuyama,[97] afforded a full conversion to *ent*-neopinone **1**, which matched with

authentic samples. Fukuyama[97] reported isomerization of neopinone obtained from the cyclization to codeinone followed by reduction of the latter to codeine. Threrefore the attainment of *ent*-neopinone **1** also formalizes the synthesis of *ent*-codeinone and *ent*-codeine.

4. Conclusions and Future Work

In the course of the present studies, we employed the *cis*-cyclohexadienediol obtained from the enzymatic dihydroxylation of β-bromoethylbenzene in a 15 step, from β-bromoethylbenzene, synthesis of *ent*-neopinone. The functionalized *cis*-cyclohexadienediol was responsible for controlling the stereoselectively of the crucial Mitsunobu coupling and intramolecular Heck reaction setting the C5 and quartenary C13 stereocenters. We also investigated several approaches for construction of phenantharene core of morphine alkaloids. Finally settling on a sequence consisting of aldol condensation and subsequent 1,6-addition. During these investigations the key issue was the incompatibility of protecting groups. This resulted in poor control of selective deprotection resulting in unintended byproduct formation. In future work, proper choice of protecting groups or ideally the use of no protecting groups could lead to a shorter and more efficient route. This would also allow for further investigation of the Mannich approach, as we could never generate the proposed intermediate because of the protecting group incompatibility. Another approach to close the C9-C14 bond could be done through a carbonyl-ene reaction by treating aldehyde **228** with various Brønsted and Lewis acids to possibly furnish the allyl silyl ether **230**, which could be converted to *ent*-neopinone by a sequence of mesylation, deprotection, oxidation and finally the 1,6 addition to close the D ring. Aldehyde **228** could be obtained via a similar synthetic route to the one discussed previously with the choice of acid stable protecting groups such as the FMoc and TIPS.



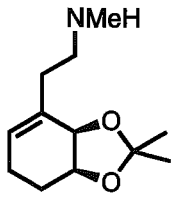
Scheme 33. Proposed carbonyl-ene closure of C9-C14 bond

5. Experimental Section

General

Reactions were carried out under inert atmosphere in oven dried glassware unless stated otherwise. Solvents were distilled: CH_2Cl_2, DMF, *i*Pr_2NEt; and pyridine from CaH_2; MeOH from magnesium methoxide; THF from Na/benzophenone; toluene from Na. Qualitative TLC was done with precoated silica gel aluminium sheets (EMD silica gel 60 F_{254}); detection by UV or by spraying with "CAM" solution (5 g of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 1 g of $Ce(SO_4)_2$, 100 ml of 10% H_2SO_4) or 0.5% aqueous $KMnO_4$ solution followed by heating. Column chromatography was performed using silica gel SiliaFlash P60 from Silicycle (40–66 μm). Optical rotation was measured in a 1-dm cell at 20-25 °C and 589 nm; concentration *c* in g/100 ml. IR spectra were recorded as ca. 2% solutions in $CHCl_3$ or as a thin film. ^1H NMR and ^{13}C NMR spectra were recorded at 300 or 600 MHz and 75 or 150 MHz, respectively, and were calibrated to the solvent signal or tetramethylsilane; the chemical shifts are reported in ppm. Mass spectra were recorded on Kratos/MsI Concept 1S mass spectrometer at Brock University. Combustion analyses were performed by Atlantic Microlabs, Norcross, GA.

2-(2,2-Dimethyl-3a,6,7,7a-tetrahydrobenzo[d][1,3]dioxol-4-yl)-*N*-methylethanamine (196).

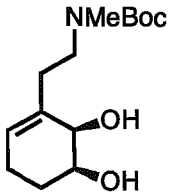


196

A solution of diol **192**Error! Bookmark not defined. (45.2g, 205 mmol) in acetone 400 ml) was treated with 2,2,-dimethoxypropane (37.6 ml, 307 mmol) and *p*TsOH. The reaction was stirred for 4 h at room temperature whereupon the solvent was evaporated. The residue was diluted with H_2O (50 ml) and extracted with CH_2Cl_2 (3 x 200 ml). The combined organic layers were washed with saturated aqueous Na_2CO_3 solution (2 x 20 ml), brine, dried (Na_2SO_4), filtered, and evaporated to yield bromide **195** (46.1 g) as a clear colorless oil, which was used without further purification. Bromide **195** (10.1 g, 38.3 mmol) was dissolved in THF (35 ml) and transferred to a 200 ml thick-walled reaction vessel containing K_2CO_3 (2.64 g, 19.1 mmol) and a magnetic stirring bar. The reaction vessel was cooled to -40 °C, and the solution was saturated with methylamine by passing gaseous methylamine from a lecture bottle through the solution for 15 min. The reaction vessel was sealed, and the mixture was stirred at 25 °C for 18 h. The mixture was cooled to -40 °C before the vessel was opened. Potassium salts were removed by filtration and rinsed with CH_2Cl_2. The solvent was evaporated to obtain amine **192** (7.6 g, 94%), which was used without further purification. R_f (AcOEt/MeOH/aqueous NH_3 7:3:1) 0.3; Mp 143-147 °C (oxalate salt); $[\alpha]_D^{24}$ = 25.8 (*c* 1, MeOH); IR (film): n 3324 (w), 2983 (s), 2932 (s), 2844 (s), 2790 (m), 1674 (m), 1563 (w), 1443 (m), 1367 (s), 1242 (s), 1221 (s), 1156 (m), 1077 (s), 1030 (s), 869 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ

5.63 (s, 1H); 4.34 (d, *J*= 5.5 Hz, 1H), 4.27 (td, *J* = 5.8, 3.2 Hz, 1H), 2.78-2.72 (m, 2H), 2.41 (s, 3H), 2.38-2.31 (m, 1H), 2.25 (q, *J* = 7.4 Hz, 1H), 2.14 (dddd, *J* = 9.0, 7.3, 3.9, 1.7 Hz, 1H), 1.91 (t, *J* = 5.3 Hz, 1H), 1.86-1.79 (m, 1H), 1.75-1.69 (m, 1H), 1.48 (s, 1H), 1.36 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 133.97, 126.58, 108.24, 73.64, 73.47, 49.81, 36.32, 34.28, 27.91, 26.46, 25.56, 20.80; LRMS-EI (*m/z*): M^+ 196 (3), 153 (14), 136 (5), 44 (100); Anal. calcd. for $C_{12}H_{21}NO_2 \cdot (COOH)_2$: C, 55.80; H, 7.69; found C, 55.75; H, 7.66.

***tert*-Butyl 2-((5*S*,6*R*)-5,6-dihydroxycyclohex-1-enyl)ethyl(methyl)carbamate (180).**

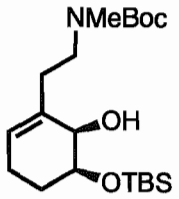


180

A solution of acetonide **196** (7.02 g, 33.2 mmol) in EtOH (40 ml) and H_2O (4 ml) was treated with 3M HCl (16.6 ml, 49.8 mmol). The reaction mixture was stirred for 4 h, treated with $NaHCO_3$ (42 g, 500 mmol), and stirred vigorously for 1 h. Then Boc anhydride (10.9 g, 49.8 mmol) was added, reaction mixture was stirred for additional 4 h, filtered, and evaporated. The residue was diluted with H_2O (25 ml) and extracted with CH_2Cl_2 (3 x 20 ml). The combined organic layers were washed with saturated aqueous NH_4Cl solution (2 x 10 ml), brine, dried (Na_2SO_4), filtered and evaporated. Flash column chromatography (hexanes/AcOEt 6:1 → 1:2) afforded **180** (6.48 g, 72%) as a colorless oil. R_f(hexanes/AcOEt 1:1) 0.20; $[\alpha]_D^{23}$ = -95.5° (*c*

0.75, $CHCl_3$); IR (film): n 3394 (s), 2975 (s), 2931 (s), 1674 (s), 1483 (s), 1353 (s), 1397 (s), 1366 (s), 1308 (m), 1247 (m), 1220 (m), 1160 (s), 1075 (m), 1053 (m), 989 (m), 945 (w), 919 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 5.43 (s, 1H), 4.87 (s, 1H), 3.96 (s, 2H), 3.56 (s, 1H), 2.99 (d, J = 8.8 Hz, 1H), 2.91 (s, 1H), 2.86 (s, 3H), 2.42-2.30 (m, 1H), 2.18 (d, J = 13.4 Hz, 1H), 2.03 (s, 2H), 1.74-1.63 (m, 1H), 1.60-1.45 (m, 1H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz): 157.0, 133.9, 128.8, 79.9, 70.0, 69.8, 48.3, 34.8, 34.0, 28.3, 25.4, 24.8; LRMS-EI (*m/z*): M^+ 271 (1), 197 (3), 171 (1), 153 (9), 144 (29), 110 (23), 88 (16), 57 (88), 44 (100); HRMS-EI (*m/z*): M^+ calcd. for $C_{14}H_{25}NO_4$: 271.1784, found 271.1796.

tert-Butyl 2-((5*S*,6*R*)-5-(_tert_-butyldimethylsilyloxy)-6-hydroxycyclohex-1-enyl)ethyl(methyl)carbamate (5).

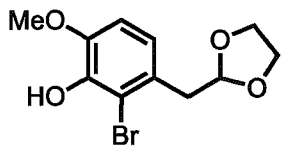


5

A solution of carbamate **180** (7.76 g, 28.6 mmol) and imidazole (3.89 g, 57.2 mmol) in CH_2Cl_2 (50 ml) was treated with TBSCl (4.75 g, 31.5 mmol) at -78 °C, the reaction mixture was left to warm slowly to 25 °C overnight and treated with saturated aqueous NH_4Cl solution (15 ml). After extraction with CH_2Cl_2 (3 x 100 ml), the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (20 ml), brine (20 ml), dried ($MgSO_4$), filtered, and evaporated. Flash column chromatography (hexanes/AcOEt 3:1) afforded **5** (8.54 g, 77 %) as a clear colorless

oil. R_f (CH_2Cl_2/AcOEt, 96:4) 0.47; $[\alpha]_D^{24}$ = -22.6 (*c* 0.5, $CHCl_3$); IR (film): n 3556 (w), 3475 (w), 2953 (s), 2857 (s), 1692 (s), 1472 (s), 1392 (s), 1253 (s), 1085 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz, mixture of rotamers): δ 5.54 (s, 1H), 5.52 (s, 1H), 3.98 (s, 1H), 3.90 (s, 1H), 3.79 (s, 1H), 3.77 (s, 1H), 3.26–3.20 (m, 2H), 2.85 (s, 3H), 2.82 (s, 3H), 2.39–2.32 (m, 2H), 2.30–2.23 (m, 2H), 2.13 (br s, 2H),1.98 (br s, 2H) 1.80–1.72 (m, 2H),1.54 (s, 2H),1.44 (s,18H), 0.9 (s,18H), 0.11 (s, 6H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 155.7, 134.8, 126.6, 79.0, 71.0, 68.8, 48.4, 47.2, 34.1, 33.3, 32.8, 28.4, 25.8, 25.4, 25.3, 24.3, 24.1, 18.1, -4.4, -4.8; LRMS-EI (*m/z*): M^+ 228 (21), 197 (21), 136 (12), 74 (22), 73 (15), 57 (63), 44 (100); HRMS-EI (*m/z*): $[M-57]^+$ calcd. for $C_{12}H_{30}NO_4Si$: 328.1944, found 328.1946; Anal. calcd for $C_{20}H_{39}NO_4Si$: C, 62.10, H,10.22; found C, 62.29, H,10.19.

2-Bromo-3-(1,3-dioxolan-2-ylmethyl)-6-methoxyphenol (191).



191

A solution of bromoisovanillin **110** (10.0g, 43.4 mmol) in CH_2Cl_2 (300 ml) was cooled to 0 °C and treated with *i*Pr_2NEt (15.1 ml, 86.7 mmol) and MOM-Cl (4.94 ml, 65.1 mmol). Reaction mixture was stirred for 3 h while the light yellow solution turned clear. The reaction mixture was diluted with H_2O (100 ml), the layers were separated and the aqueous layer was extracted with AcOEt (3 x 40 ml). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and

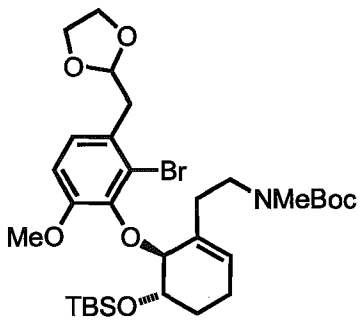
evaporated to yield crude **188** as a light yellow/brown solid (12.2 g) which was used without further purification. R_f (hexanes/AcOEt 1:1) 0.69.

A solution of $Ph_3P^+CH_2OCH_3Cl^-$ (23.1 g, 67.2 mmol) in THF (125 ml) was cooled to -78°C, treated with *t*BuLi (35.9 ml, 61.1 mmol) dropwise over 10 min, and stirred for 15 min. The solution was warmed to 0 °C and treated with crude **188** (16.3 g, 61.1 mmol) in THF (17 ml) dropwise over 5 min while the deep orange solution turned to a deep yellow suspension. The suspension was refluxed for 3.5 h, cooled to 25 °C, diluted with AcOEt (100 ml), and washed with H_2O (100 ml). The aqueous layer was extracted with AcOEt (3 x 50 ml) and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and evaporated to yield crude **189** as a yellow solid (30.8 g) which was used without further purification.

A solution of crude **189** (32.2 g, 106 mmol) in THF (300 ml) was treated with *p*TsOH (10.1 g, 53.0 mmol), ethylene glycol (29.6 ml, 530 mmol), and refluxed for 2 h. Reaction mixture was cooled to 25 °C, concentrated, diluted with AcOEt (150 ml), and washed with H_2O (2 x 20 ml). Organic layer was washed with brine, dried ($MgSO_4$), filtered and evaporated. The residue was dissolved in CH_2Cl_2 (100 ml) and extracted with 0.5M NaOH (3 x 10 ml). The combined aqueous layers were neutralized with 1M HCl to pH 7 and extracted with AcOEt (3 x 15 ml). Combined organic layers were washed saturated aqueous $NaHSO_3$ solution (5 x 15 ml), brine, dried ($MgSO_4$), filtered and evaporated to yield **191** (16.2 g, 76% from **110**) as a light yellow solid. Sample for analysis was recrystallized from AcOEt/hexanes. R_f (hexanes/AcOEt 1:1) 0.59; Mp 118-120 °C (AcOEt/hexanes); IR ($CHCl_3$): n 3370 (w), 2959 (w), 2892 (w), 1607 (w), 1577 (w), 1490 (s), 1465 (w), 1441 (m), 1404 (w),

1362 (w), 1336 (w), 1283 (s), 1232 (m), 1199 (w), 1169 (w), 1130 (m), 1034 (s), 986 (w), 942 (w), 820 (w), 802 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 6.88 (d, J = 8.3 Hz, Ar H), 6.79 (d, J = 8.3 Hz, 1H), 5.95 (s, exchange with D_2O, 1H), 5.12 (t, J = 4.9 Hz, 1H), 4.03-3.80 (m, 4H), 3.89 (s, 3H), 3.09 (d, J = 4.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 145.97, 143.20, 128.86, 111.36, 122.13, 109.66, 103.51, 65.05, 56.41, 40.17; LRMS-EI (*m/z*): M^+ 289 (1), 73 (100), 45 (14); HRMS-EI (*m/z*): M^+ calcd. for $C_{11}H_{13}BrO_4$: 287.9997, found 287.9994; Anal. calcd. for $C_{11}H_{13}BrO_4$: C, 45.70, H, 4.53; found: C, 45.99, H, 4.47.

tert-Butyl 2-((5'*S*,6'*S*)-6'-(3"-((1,3-dioxolan-2-yl)methyl)-2"-bromo-6"-methoxyphenoxy)-5'-(_tert_-butyldimethylsilyloxy)cyclohex-1'-enyl)ethyl(methyl)carbamate (197).



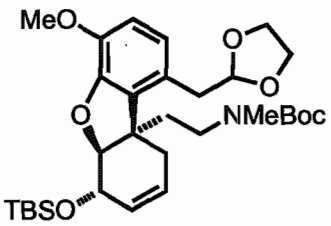
197

An orange solution of DIAD (7 ml, 35.6 mmol) in degassed THF (45 ml) was cooled to -10 °C and treated with PBu_3 (9.5 ml, 38.5 mmol) at one portion. The resulting pale yellow solution was stirred for 25 min at -10 °C and transferred over 35 min into a chilled (4 °C) solution of alcohol **5** (10.6 g, 27.4 mmol) and phenol **191** (8.7 g, 30.2 mmol) in degassed THF (90 ml). The mixture was allowed to reach 25 °C,

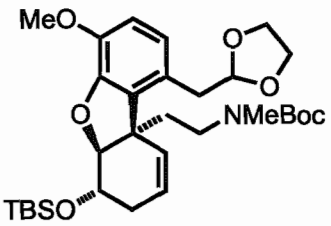
stirred for 12 h, and evaporated. The residue was adsorbed on silica gel and subjected to chromatography (hexanes/AcOEt 8:1) obtain **197** (13.8 g, 76%) and recovered phenol **191** (664 mg, 8%). *Data for* **197**: Yellow oil; R_f (hexanes/AcOEt 2:1) 0.75; $[\alpha]_D^{20}$ = + 43.7 (*c* 0.125, $CHCl_3$); IR ($CHCl_3$): n 3294 (w), 2930 (s), 2857 (m), 1736 (w), 1697 (s), 1594 (w), 1482 (s), 1441 (m), 1393 (m), 1365 (m), 1293 (m), 1252 (s), 1171 (s), 1137 (s), 1105 (m), 1085 (m), 1035 (s), 1007 (m), 943 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz, two rotamers): 7.04 (d, *J* = 8.3 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 5.80, 5.77 (2 br. s, 1H), 5.06 (t, *J* = 4.9 Hz, 1H), 4.48 (br. s, 1H), 4.00-3.92 (m, 3H), 3.87-3.78 (m, 2H), 3.83 (s, 3H), 3.55 (br. s, 0.4H), 3.41 (br. s, 0.6H), 3.22–3.15 (m, 1H), 3.13 (dd, *J* = 14.0, 4.5 Hz, 1H), 3.07 (dd, *J* = 14.0, 5.3 Hz, 1H), 2.81 (br. s, 3H), 2.52 (br. s, 0.4 H), 2.46 (br. s, 0.6H), 2.42-2.35 (m, 1H), 2.25-2.13 (m, 2H), 2.02-1.94 (m, 1H), 1.67-1.60 (m, 1H), 1.44 (s, 9H), 0.72 (s, 9H), -0.18, -0.21 (2 s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz, 2 rotamers): 155.9, 155.7, 152.0, 144.6, 131.4, 129.2, 121.3, 131.4, 126.2, 111.1, 103.5, 79.8, 79.6, 79.1, 67.5, 65.0, 55.8, 49.1, 48.3, 40.6, 35.3, 35.1, 33.7, 32.9, 28.6, 25.8, 25.3, 20.8, 18.1, -5.1; LRMS-EI (*m/z*): M^+ 656 (1), 368 (8), 312 (45), 268 (39), 237 (52), 180 (8), 136 (28), 105 (10), 73 (100), 57 (58), 44 (35); HRMS-EI (*m/z*): M^+ calcd. for $C_{31}H_{51}BrNO_7Si$: 656.2540, found 656.2595; Anal. calcd. for $C_{31}H_{51}BrNO_7Si$: C, 56.70; H, 7.67; found C, 56.95; H, 7.77.

***tert*-butyl 2-((5a*S*,6*S*,9a*R*)-1-((1,3-dioxolan-2-yl)methyl)-6-(*tert*-butyldimethylsilyloxy)-4-methoxy-5a,6,9,9a-tetrahydrodibenzo[*b*,*d*]furan-9a-yl)ethyl(methyl)carbamate (198).** And ***tert*-Butyl 2-((5a*S*,6*S*,9a*R*)-1-((1,3-**

dioxolan-2-yl)methyl)-6-(*tert*-butyldimethyl-silyloxy)-4-methoxy-5a,6,7,9a-tetrahydrodibenzo[*b*,*d*]furan-9a-yl)ethyl(methyl)- carbamate (199)



198

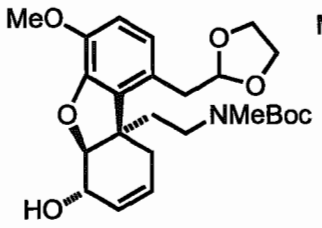


199

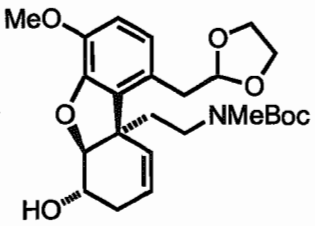
A solution of **197** (6.38 g, 9.7 mmol) in degassed toluene (60 ml) was treated with K_2CO_3 (2.01 g, 14.6 mmol), $Pd_2(dba)_3$ (888 mg, 0.97 mmol), and tBu$_3$P (393 mg, 1.94 mmol), immersed in a preheated oil bath (110 °C), and stirred for 16 h. The reaction mixture was filtered through a plug of Celite (washing with CH_2Cl_2) and evaporated. Flash column chromatography (hexanes/AcOEt 4:1) afforded an inseparable mixture of **199** and **198** (**199/198** ≈ 5:1, 4.82 g, 86%) as a brown oil. R_f (hexanes/AcOEt 2:1) 0.59; $[\alpha]_D^{20}$ = +34.8 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): n 3010 (w), 2956 (m), 2931 (m), 2895 (w), 2857 (w), 1730 (w), 1683 (m), 1626 (w), 1584 (w), 1506 (m), 1482 (w), 1472 (w), 1438 (w), 1401 (w), 1394 (w), 1367 (w), 1321 (w), 1282 (w), 1258 (m), 1221 (s), 1216 (s), 1213 (s), 1210 (s), 1155 (m), 1127 (m), 1048 (w), 1009 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.78 (d, J = 8.3 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 6.01-5.97 (m, 1H), 5.73-5.68 (m, 1H), 5.05 (m, 1H), 4.45 (m, 1H), 4.01 (m, 2H), 3.90-3.86 (m, 3H), 3.82 (s, 3H), 3.07 (m, 1H), 3.00-2.88 (m, 2H), 2.77 (s, 3H), 2.28-2.18 (m, 1H), 2.13-1.95 (m, 1H), 1.92-1.83 (m, 2H), 1.57 (m, 2H), 1.43 (s, 9H), 0.89 (s, 9H), 0.13 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 155.5, 146.1, 143.9, 132.3, 129.4, 124.8, 123.1, 111.7, 104.7, 104.5, 89.8, 79.4, 68.4, 65.0,

64.9, 55.8, 51.4, 45.2, 37.5, 36.3, 35.4, 34.2, 30.8, 29.7, 28.4, 25.8, 25.7, 18.1; LRMS-EI (*m/z*): 310 (7), 237 (1), 184 (10), 139 (4), 91 (22), 73 (66), 57 (80), 43 (100); HRMS-EI (*m/z*): M^+ calcd. for $C_{31}H_{49}NO_7Si$: 575.3278, found 575.3276.

***tert*-butyl 2-((5a*S*,6*S*,9a*R*)-1-((1,3-dioxolan-2-yl)methyl)-6-hydroxy-4-methoxy-5a,6,9,9a-tetrahydrodibenzo[*b*,*d*]furan-9a-yl)ethyl(methyl)carbamate (201).** and ***tert*-Butyl 2-((5a*S*,6*S*,9a*R*)-1-((1,3-dioxolan-2-yl)methyl)-6-hydroxy-4-methoxy-5a,6,7,9a tetrahydrodibenzo [*b*,*d*]furan-9a-yl)ethyl(methyl)carbamate (202)**



201



202

A solution of **199** and **198** (**199/198** ≈ 5:1, 4.82 g, 8.34 mmol) in THF (50 ml) was cooled to 0 °C and treated with a 1.0M solution of TBAF in THF (12.6 ml, 12.6 mmol). The mixture was stirred for 16 h at 25 °C, diluted with AcOEt (40 ml), and washed with H_2O (25 ml). The aqueous layer was extracted with AcOEt (3 x 45 ml) and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated. Flash column chromatography (hexanes/AcOEt 4:1 → 1:1) afforded **201** (593 mg, 15%) as a light yellow foam and **202** (3.14 g, 82%) as a light yellow foam.

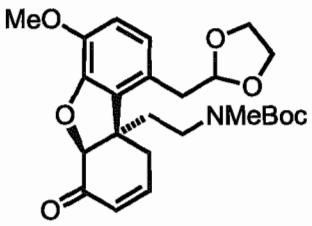
Data for **201**: R_f (hexanes/AcOEt 1:2) 0.58; $[\alpha]_D^{20}$ = +11.7 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): n 3596 (w), 3024 (w), 3010 (m), 2979 (m), 2935 (m), 2895 (m), 2840 (w), 1729 (w), 1683 (s), 1626 (w), 1585 (w), 1507 (s), 1482 (m), 1463 (m), 1453 (m), 1436 (m),

1401 (m), 1367 (m), 1344 (w), 1320 (w), 1282 (m), 1167 (s), 1154 (s), 1097 (m), 1047 (m), 1020 (m), 987 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz, 2 rotamers): δ 6.85 (d, *J*= 8.4 Hz, 1H), 6.75 (d, *J*= 8.4 Hz, 1H), 5.94 (br. s, 1H), 5.89 (br. s, 1H), 5.07 (br. s, 1H), 4.36 (br. d, *J*= 6.4 Hz, 1H), 4.30-4.25 (m, 1H), 4.02-3.95 (m, 2H), 3.90-3.80 (m, 2H), 3.85 (s, 3H), 3.24 (ddd, *J* = 13.9, 12.3, 4.0 Hz, 1H), 2.98 (dd, *J* = 14.4, 4.3 Hz, 1H), 2.96-2.90 (m, 1H), 2.84-2.60 (m, 3H), 2.46 (d, *J*= 15.1 Hz, 1H), 2.15-2.00 (m, 1H), 1.92-1.77 (m, 1H), 1.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz, 2 rotamers): δ 155.56, 146.94, 143.37, 131,75, 124.85, 130.52, 127.49, 123.41, 111.62, 104.76, 92.96, 79.65, 70.39, 65.09, 65.01, 55.93, 48.60, 45.48, 40.08, 35.64, 35.48, 34.43, 28.58; LRMS-FAB (*m/z*): $[M+H]^+$ 462 (7), 344 (38), 285 (17), 241 (9), 159 (7), 103 (36), 73 (100), 57 (73); HRMS-FAB (*m/z*): $[M+H]^+$ calcd. for $C_{25}H_{36}NO_7$: 462.2492, found: 462.2428.

Data for **202**: R_f (hexanes/AcOEt 1:2) 0.26; $[\alpha]_D^{20}$ +9.5 (*c* 3.2, $CHCl_3$); IR (film): n 3629 (m), 3018 (s), 1732 (m), 1683 (s), 1625 (w), 1584 (w), 1507 (m), 1400 (m), 1367 (m), 1318 (w) 1280 (m), 1216 (s), 1156 (m), 1097 (m), 1047 (m), 978 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 2 rotamers): δ 6.81 (d, *J* =8.3 Hz, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 6.03 (dd, *J* = 9.8, 1.5 Hz, 1H), 5.78 (ddd, *J* = 9.8, 5.7, 2.3 Hz, 1H), 5.04 (dd, *J* = 6.0, 3.8 Hz, 1H), 4.55-4.37 (br. s, 1H), 4.05-3.95 (m, 2H), 3.90-3.80 (m, 2H); 3.85 (s, 3H), 3.47-3.20 (m, 1H), 3.06 (dd, *J* = 14.3, 3.4 Hz, 1H), 2.94-2.82 (m, 1H), 2.89 (dd, *J* = 14.3, 6.0 Hz, 1H), 2.77 (s, 3H), 2.45-2.30 (m, 1H), 2.19-2.03 (m, 1H), 2.03-1.78 (m, 2H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 155.61, 145.76, 144.18, 129.29, 125.10, 129.49, 124.66, 123.92, 111.80, 104.67, 90.64, 90.12, 79.67, 68.18, 65.10, 65.06, 56.03, 51.84, 36.59, 34.41, 29.41, 28.61; LRMS-EI (*m/z*): M^+ 461 (6), 388 (3), 340 (8), 285 (16), 271 (6), 241 (2), 213 (8), 142 (31), 103 (20), 84 (31), 73 (100), 57

(81); HRMS-EI (*m/z*): M^+ calcd. for $C_{25}H_{35}NO_7$: 461.2414, found 461.2414; Anal. calcd. for $C_{25}H_{35}NO_7$: C, 65.06; H, 7.64; found C, 64.94; H, 7.67.

tert-Butyl 2-((5a*S*,9a*S*)-1-((1,3-dioxolan-2-yl)methyl)-4-methoxy-6-oxo-5a,6,9,9a-tetrahydrodibenzo[*b*,*d*]furan-9a-yl)ethyl(methyl)carbamate (203).

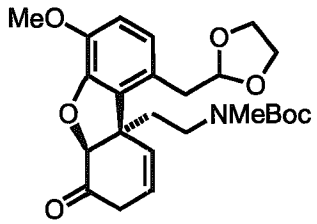


203

A solution of alcohol **201** (229 mg, 0.496 mmol) in DMF (10 ml) was cooled to 0 °C and treated with IBX (139 mg, 0.496 mmol). The reaction mixture was stirred for 16 h at 25 °C, diluted with H_2O (4 ml), and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (3 x 8 ml). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated. Flash column chromatography (hexanes/AcOEt, 3:1 → 1.5:1) afforded **201** (12 mg, 5%) as a light yellow foam and **203** (159 mg, 70%) as a light yellow oil. R_f (hexanes/AcOEt 1:2) 0.32; $[\alpha]_D^{20}$ = + 91.3° (*c* 1.415, $CHCl_3$); IR (film): n 2979 (w), 1685 (s), 1625 (w), 1507 (m), 1393 (w), 1366 (w), 1284 (w), 1148 (m), 1044 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.92 (m, 1H), 6.82 (d, *J*= 8.4, 1H), 6.73 (d, *J*= 8.4, 1H), 6.20 (d, *J*= 9.6, 1H), 5.05 (t, *J*= 4.5, 1H), 4.66 (br s, 1H), 3.98-3.88 (m, 2H), 3.87-3.79 (m, 6H), 3.34-3.24 (m, 1H), 3.17-3.03 (m, 1H), 3.03-2.94 (m, 2H), 2.88-2.82 (m, 1H), 2.77 (s, 4H), 2.15-2.09 (m, 2H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 155.36, 148.63, 147.28, 143.69, 128.96, 124.57, 124.04, 112.52, 104.55, 86.31, 79.80, 65.03, 64.97, 60.39,

56.05, 49.62, 45.23, 38.45, 35.77, 34.27, 28.45, 21.05, 14.20; LRMS-EI (*m/z*): M^+ 386(2), 359(12), 301(21), 257(14), 216(5), 190(4), 149(4), 103(7), 84(20), 73(100), 57(33), 43(82); HRMS-EI (*m/z*): M^+ calcd. for $C_{25}H_{33}NO_7$: 459.2257, found 459.2260.

tert-Butyl 2-((5a*S*,6*S*,9a*R*)-1-((1,3-dioxolan-2-yl)methyl)-6-hydroxy-4-methoxy-5a,6,7,9a-tetrahydrodibenzo[b,d]furan-9a-yl)ethyl(methyl)carbamate (204).

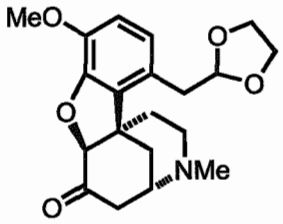


204

A solution of **202** (499 mg, 1.08 mmol) in AcOEt (20 ml) was treated with IBX (457 mg, 1.63 mmol), the resulting suspension was stirred for 6 h at 80 °C, and cooled to 0 °C. Filtration through Celite (washing with cold AcOEt) afforded crude **204** (601 mg) which was used in the next step without further purification. R_f (hexanes/AcOEt 1:1) 0.35; IR ($CHCl_3$): n 3025 (w), 3010 (m), 2979 (m), 2934 (m), 2894 (w), 2840 (w), 1736 (m), 1683 (s), 1627 (w), 1583 (w), 1508 (m), 1481 (m), 1462 (m), 1454 (m), 1428 (m), 1399 (m), 1367 (m), 1319 (w), 1283 (s), 1168 (s), 1154 (s), 1092 (w), 1078 (w), 1042 (m), 1017 (m), 984 (w), 944 (w), 909 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.84 (d, *J* = 8.3 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.03 (br. s, 1H), 5.81 (dt, *J* = 9.8, 3.8 Hz, 1H), 5.03 (br. t, *J* ≈ 4.5 Hz, 1H), 4.99 (br. s, 0.33H), 4.75 (br. s, 0.66H), 4.03–3.94 (m, 2H), 3.94–3.80 (m, 2H), 3.87 (s, 3H), 3.30–2.87 (m, 6H),

2.81 (s, 3H), 2.23–2.02 (m, 2H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz, 2 rotamers): δ 146.90, 143.96, 129.75, 129.40, 124.56, 124.16, 124.16, 123.64, 112.49, 104.57, 87.81, 87.47, 79.93, 65.08, 56.24, 45.34, 44.83, 37.64, 37.20, 36.43, 34.40, 34.44, 28.58; LRMS-FAB (*m/z*): M^+ 459 (1), 85 (67), 83 (100), 73 (81), 57 (27), 47 (19), 44 (22), 41 (18); HRMS-EI (*m/z*): M^+ calcd. for $C_{25}H_{33}NO_7$: 459.2257, found 459.2252.

(4*S*, 6a*S*, 11b*R*)-11-(1,3-Dioxolan-2-ylmethyl)-8-methoxy-3-methyl-2,3,4,5-tetra-hydro-1*H*-4,11b-methano[1]benzofuro[3,2-*d*]azocin-6-one (205).

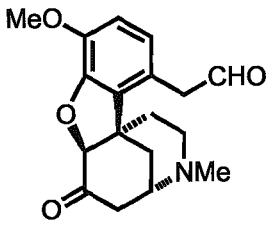


205

A solution of crude **204** (theoretical content 1.08 mmol) in CH_2Cl_2 (8 ml) was treated with TFA (2 ml), the mixture was stirred for 1 h, and poured into saturated aqueous Na_2CO_3 solution (30 ml) containing solid Na_2CO_3 (6 g). The biphasic mixture was stirred for 10 min (effervescence), diluted with CH_2Cl_2 (30 ml) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 ml). The combined organic layers were washed with brine (40 ml), dried (Na_2SO_4), and evaporated. Flash column chromatography (AcOEt/MeOH 6:1) afforded **205** (217 mg, 56% from **202**) as a brown foam. R_f ($CHCl_3$/MeOH/aqueous NH_3 92:8:1) 0.52; IR ($CHCl_3$): n 3021 (m), 3011 (m), 2959 (m), 2935 (m), 2893 (m), 2794 (w), 1727 (s), 1628 (w), 1584 (w), 1508 (s), 1475 (w), 1462 (w), 1452 (m), 1452 (m), 1437 (m),

1401 (m), 1377 (w), 1359 (w), 1340 (w), 1283 (s), 1267 (m), 1167 (m), 1142 (s), 1115 (s), 1017 (s), 990 (m), 951 (w), 944 (w), 924 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.82 (d, *J* = 8.5 Hz, 1H), 6.73 (d, *J* = 8.5 Hz, 1H), 5.02 (t, *J* = 4.8 Hz, 1H), 4.72 (s, 1H), 4.00-3.90 (m, 2H), 3.90-3.79 (m, 2H), 3.83 (s, 3H); 3.51 (m, 1H), 3.01 (dd, *J* = 14.5, 4.7 Hz, 1H), 2.97 (dd, *J* = 14.5, 5.1 Hz, 1H), 2.96-2.85 (m, 1H), 2.71-2.55 (m, 2H), 2.50-2.30 (m, 2H), 2.34 (s, 3H), 1.85 (br. d, *J* = 12.9 Hz, 1H), 1.70 (dt, *J* = 13.2, 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 205.76, 147.02, 143.69, 131.30, 124.72, 124.13, 111.98, 104.81, 89.16, 65.09, 55.98, 49.39, 46.92, 42.96, 36.28, 35.67, 34.25; LRMS-EI (*m/z*): 290 (18), 288 (18), 217 (21), 215 (22), 74 (11), 73 (100), 45 (41); HR MS-EI (*m/z*): M^+ calcd. for $C_{20}H_{25}NO_5$: 359.1733, found 359.1740. Anal. calcd. for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01; found C, 66.83; H, 7.02.

[(4*S*,6a*S*,11b*R*)-8-Methoxy-3-methyl-6-oxo-2,3,4,5,6,6a-hexahydro-1H-4,11b-methano[1]benzofuro[3,2-d]azocin-11-yl]acetaldehyde (206).

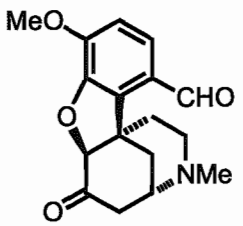


206

A mixture of **205** (231 mg, 0.643 mmol) and oxalic acid (159 mg, 1.77 mmol) in H_2O (6 ml) was stirred at 40 °C for 13 h, cooled to 25 °C, poured into saturated aqueous $NaHCO_3$ solution (15 ml), and extracted with $CHCl_3$ (3 x 15 ml). The combined organic layers were washed with brine (15 ml), dried ($MgSO_4$), and evaporated to

get crude aldehyde **206** (227 mg) which was used without further purification. A sample was purified by flash column chromatography ($CHCl_3$/MeOH/aqueous NH_3 92:8:1). Colorless oil; R_f ($CHCl_3$/MeOH/aqueous NH_3 92:8:1) 0.52; ^1H NMR ($CDCl_3$, 600 MHz, crude): δ 9.70 (br. t, *J* = 1.9 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 6.66 (d, *J* = 8.3 Hz, 1H), 4.76 (s, 1H), 3.86 (s, 3H), 3.78 (dd, *J* = 17.0, 1.9 Hz, 1H), 3.72 (dd, *J* = 17.0, 1.9 Hz, 1H), 3.53-3.48 (m, 1H), 2.96-2.91 (m, 1H); 2.68 (d, *J* = 17.4 Hz, 1H), 2.50-2.30 (m, 3H), 2.35 (s, 3H), 2.19 (br. d, *J* = 12.8 Hz, 1H), 1.89-1.84 (m, 1H), 1.71 (dt, *J* ≈ 12.8, 2.3 Hz, 1H); LRMS-EI *(m/z)*: M+ 315 (3), $[M\text{-}OH]^+$ 298 (21), $[M\text{-}H_2O]^+$ 297 (100), 282 (11), 229 (18), 214 (20), 188 (10), 43 (11), 42 (14); HRMS-EI *(m/z)*: M^+ calcd. for $C_{18}H_{21}NO_4$: 315.1471, found 315.1469.

(4*S*,6a*S*,11b*R*)-8-Methoxy-3-methyl-6-oxo-2,3,4,5,6,6a-hexahydro-1H-4,11b-methano[1]benzofuro[3,2-d]azocine-11-carbaldehyde (207).

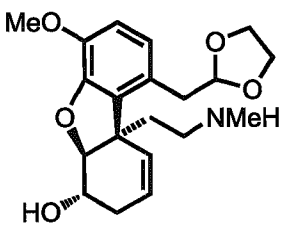


207

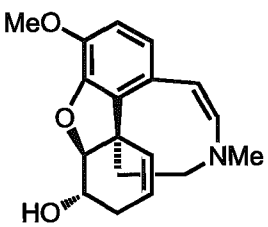
A solution of crude aldehyde **206** (4 mg) in MeCN (0.2 ml) and H_2O (0.2 ml) was treated with concentrated HCl until the pH reached 1, the mixture was stirred at 40 °C for 22 h, cooled to 25 °C, poured into saturated aqueous $NaHCO_3$ solution (5 ml), and extracted with $CHCl_3$ (4 x 5 ml). The combined organic layers were washed with brine (5 ml), dried ($MgSO_4$), and evaporated to furnish crude **207** (4 mg). A pure sample was obtained by flash column chromatography (AcOEt/MeOH 7:1 → 5:1). R_f

(AcOEt/MeOH 5:1) 0.33; IR ($CHCl_3$): n 3027 (w), 3012 (w), 2963 (m), 2964 (m), 2845 (w), 2789 (w), 2745 (w), 1726 (s), 1691 (s), 1615 (s), 1574 (m), 1507 (m), 1447 (m), 1438 (m), 1410 (w), 1377 (w), 1340 (w), 1293 (s), 1270 (m), 1260 (m), 1169 (m), 1144 (m), 1117 (m), 1102 (m), 1066 (w), 1054 (w), 1017 (m), 981 (w), 953 (w), 927 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 9.91 (s, 1H), 7.43 (d, *J* = 8.3 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 4.93 (s, 1H), 3.95 (s, 3H), 3.51–3.46 (m, 1H), 3.05 (td, *J* = 12.5, 5.3 Hz, 1H), 2.95 (br. dd, *J* = 12.8, 4.2 Hz 1H), 2.85 (br. d, *J* = 12.1 Hz, 1H), 2.67 (br. d, *J* = 17.4 Hz, 1H); 2.53 (br. t, *J* = 11.3 Hz, 1H); 2.42 (dd, *J* = 17.0, 8.7 Hz, 1H), 2.37 (s, 3H), 1.70 (br. d, *J* = 12.8 Hz, 1H), 1.54 (br. dt, *J* = 12.8, 2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 206.07, 190.54, 150.03, 148.00, 132.57, 126.45, 131.08, 110.88, 90.22, 56.17, 55.76, 50.45, 46.38, 43.10, 34.34, 34.18; LRMS-EI (*m/z*): M^+ 301 (23), 273 (23), 272 (20), 258 (34), 231 (29), 230 (72), 215 (40), 167 (30), 150 (26), 149 (100), 112 (21), 83 (28), 71 (36), 70 (84), 69 (20), 57 (52), 55 (26), 44 (41), 43 (49), 41 (31); HRMS-EI (*m/z*): M^+ calcd. for $C_{17}H_{19}NO_4$: 301.1314, found 301.1310.

(4*S*,4a*S*,9b*R*)-9-((1,3-Dioxolan-2-yl)methyl)-6-methoxy-9b-(2-(methylamino)ethyl)-3,4,4a,9b-tetrahydrodibenzo[b,d]furan-4-ol (214) and **(4a*S*,5*S*,8a*R*,*E*)-3-Methoxy-11-methyl-4a,5,6,9,10,11-hexahydrobenzo[2,3]benzo-furo[3,4-*de*]azocin-5-ol (215).**



214



215

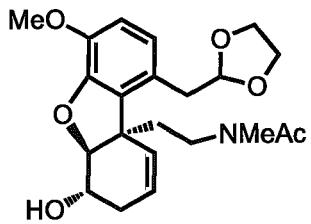
A solution of carbamate **202** (514 mg, 1.13 mmol) in CH_2Cl_2 (1 ml) was cooled to 0 °C and treated with TFA (0.25 ml) over 10 min. The mixture was stirred for 15 min, concentrated, diluted with saturated aqueous Na_2CO_3 solution (3 ml) and extracted with CH_2Cl_2 (3 x 5 ml). The combined organic layers were washed with brine (5 ml), dried ($MgSO_4$), and evaporated. Flash column chromatography (CH_2Cl_2/MeOH/aqueous NH_3 100:10:1) afforded secondary amine **214** (202 mg, 0.559 mmol, 49%) and enamine **215** (34 mg, 10 %).

Data for **214**: Colorless oil; R_f (CH_2Cl_2/MeOH/aqueous NH_3 100:10:1) 0.33; $[\alpha]_D^{20}$ = +22.8 (*c* 0.875, $CHCl_3$); IR ($CHCl_3$): n 3588 (w), 3027 (w), 2936 (m), 1624 (m), 1582 (m), 1506 (s), 1438 (m), 1280 (s), 1131 (s), 1099 (s), 1043 (s), 975 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 6.80 (d, *J* = 8.4 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.00 (d, *J* = 9.6 Hz, 1H), 5.04 (dd, *J* = 5.4, 4.2 Hz, 1H), 4.65 (d, *J* = 6.0 Hz, 1H), 4.04-4.00 (m, 3H), 3.88-3.85 (m, 2H), 3.03 (dd, *J* = 14.4, 5.4 Hz, 1H), 2.92 (dd, *J* = 14.4, 5.4 Hz, 1H), 2.78-2.71 (m, 1H), 2.60-2.54 (m, 1H), 2.38 (s, 1H), 2.31 (d, *J*= 1.8 Hz, 1H), 2.15-2.12 (m, 2H), 2.02-2.00 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 145.87, 143.71, 133.12, 129.68, 125.15, 124.54, 123.50, 111.33, 104.53, 89.46, 66.77, 64.94, 64.92, 55.82, 47.70, 41.46, 39.19, 36.82, 36.24, 35.87, 28.74; LRMS-FAB (*m/z*): $[M + H]^+$ 362 (100), 73 (45), 59 (32), 45 (12), 44 (40); HRMS-EI (*m/z*): M^+ calcd. for $C_{20}H_{27}NO_5$: 361.1889, found 361.1891. Anal. calcd. for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; found C, 66.17; H, 7.56.

Data for **215**: Ocre solid; R_f (CH_2Cl_2/MeOH/aqueous NH_3 100:10:1) 0.57; IR ($CHCl_3$): n 3593 (w), 3027 (w), 3008 (m), 2958 (m), 2932 (m), 2854 (w), 2801 (w), 1723 (w), 1690 (w), 1666 (w), 1627 (s), 1572 (w), 1503 (s), 1464 (m), 1438 (m), 1427 (m), 1415 (m), 1380 (m), 1339 (w), 1285 (s), 1263 (s), 1160 (m), 1103 (s), 1087 (s),

1074 (m), 1055 (s), 1020 (m), 1005 (m), 976 (w), 968 (w), 955 (w), 908 (w) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.66 (d, *J* = 8.5 Hz, 1H), 6.58 (d, *J* = 8.5 Hz, 1H), 6.53 (dd, *J* = 10.2, 3.0 Hz, 1H), 5.75 (d, *J* = 9.4 Hz, 1H), 5.64 (ddd, *J* ≈ 10.2, 6.4, 1.9 Hz, 1H), 4.88 (d, *J* = 9.4 Hz, 1H), 4.30 (d, *J* = 9.0 Hz, 1H), 3.85 (s, 3H), 3.82-3.69 (m, 1H), 3.61 (ddd, *J* = 15.1, 12.8, 3.4 Hz, 1H), 2.87 (s, 3H), 2.87 (s, 3H), 2.82-2.67 (m, 1H), 2.36 (dt, *J* = 16.6, 6.0 Hz, 1H), 2.10 (ddd, *J* ≈ 10.9, 2.3 Hz, 1H), 1.86 (dt, *J* = 13.0, 4.3 Hz, 1H), 1.51 (dt, *J* ≈ 13.6, 2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 145.30, 142.94, 137.41, 129.80, 129.04, 127.48, 122.83, 121.36, 111.45, 94.96, 93.82, 68.66, 55.97, 52.88, 48.47, 42.19, 30.92, 29.39; LRMS-FAB (*m/z*): $[M + H]^+$ 300 (23), M^+ 299 (54), $[M - OMe]^+$ 268 (12), 136 (23), 91 (20), 73 (100), 69 (26), 57 (57), 55 (42), 44 (30), 43 (43), 41 (37); HRMS-FAB (*m/z*): M^+ calcd. for $C_{18}H_{21}NO_3$: 299.1521, found 299.1523.

N-(2-((5a*S*,6*S*,9a*R*)-1-((1,3-Dioxolan-2-yl)methyl)-6-hydroxy-4-methoxy-5a,6,7,9a-tetrahydrodibenzo[b,d]furan-9a-yl)ethyl)-*N*-methylacetamide (217).

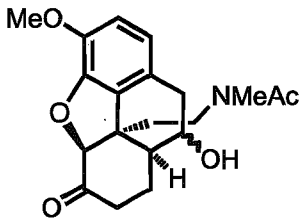


217

A solution of **214** (21 mg, 0.058 mmol) in CH_2Cl_2 (1.5 ml) and pyridine (0.1 ml, 1.239 mmol) was treated with AcCl (25 µl, 0.352 mmol) at 4 °C. The suspension was stirred 2.5 h at 4 °C and 1 h at 25 °C, diluted with CH_2Cl_2 (10 ml) and washed with

1M HCl (6 ml), saturated aqueous $NaHCO_3$ solution (6 ml), and brine (6 ml), dried ($MgSO_4$), and evaporated. The crude diacetate was pure based on ^1H NMR spectrum and was used directly in the next step. A solution of crude diacetate in 0.12M solution of MeONa in MeOH was stirred for 4 h and treated with DOWEX 50WX8-100(H^+ form). Filtration, evaporation, and liquid chromatography (AcOEt/MeOH 5:1) afforded **217** (20 mg, 87%) as a colorless oil. R_f (CH_2Cl_2/MeOH/aqueous NH_3 100:10:1) 0.51; $[\alpha]_D^{20}$ +17.5 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): n 3593 (w), 3024 (w), 3010 (m), 2937 (m), 2896 (w), 2841 (w), 1732 (w), 1633 (s), 1584 (w), 1507 (m), 1463 (w), 1439 (m), 1428 (m), 1402 (m), 1379 (w), 1362 (w), 1315 (w), 1280 (m), 1262 (m), 1255 (m), 1167 (w), 1130 (m), 1091 (m), 1049 (m), 1017 (m), 980 (w), 944 (w), 909 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, 2 rotamers): δ 6.85-6.69 (m, 2H), 6.04 (br. s, 0.6H), 6.01 (br. s, 0.4H), 5.85-5.72 (m, 1H), 5.08-4.99 (m, 1H), 4.56-4.49 (m, 0.6H), 4.35 (d, *J* = 8.5 Hz, 0.4H), 4.03-3.79 (m, 1H), 7H), 3.65-3.59 (m, 0.6H), 3.40-3.26 (m, 1.4H), 3.10-2.78 (m, 6H), 2.47-2.29 (m, 1H), 2.21-1.78 (m, 3H), 2.00 (s, 1.7H), 1.95 (1.3H). ^{13}C NMR ($CDCl_3$, 150 MHz, 2 rotamers): δ 170.49, 170.39, 145.76, 145.59, 144.14, 144.06, 132.52, 131.73, 129.19, 128.91, 125.58, 125.18, 124.74, 124.53, 124.17, 123.77, 111.90, 111.72, 104.62, 104.60, 90.75, 90.05, 67.90, 67.86, 65.11, 65.05, 56.02, 55.97, 55.95, 51.74, 51.65, 46.84, 44.10, 38.39, 36.51, 36.48, 36.46, 36.37, 33.41, 21.94, 21.06; LRMS-EI (*m/z*): M^+ 403 (1.1), 122 (18), 102 (18), 101 (27), 100 (16), 86 (11), 85 (16), 83 (23), 80 (100), 73 (35), 44 (14), 43 (50); HRMS-EI (*m/z*): M^+ calcd. for $C_{22}H_{29}NO_6$: 403.1995, found 403.2000.

***N*-(2-((2*S*,2a1*R*, 5a*S*)-2-Hydroxy-7-methoxy-5-oxo-1,2,2a,2a1,5,5a-hexahydrophenanthro[4,5-bcd]furan-2a1-yl)ethyl)-*N*-methylacetamide (218).**



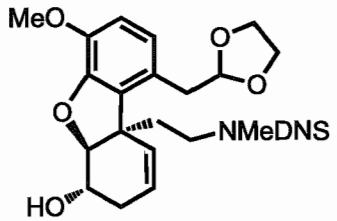
218

A suspension of **217** (30 mg, 0.074 mmol) and IBX (31 mg, 0.11 mmol) in AcOEt (2 ml) was stirred at 80 °C for 4 h, cooled to 25 °C, filtered through Celite (washing with AcOEt), and evaporated to get crude ketone (15 mg) which was used in the next step without further purification. R_f (AcOEt/MeOH 10:1) 0.30.

A solution of crude ketone (15 mg, 0.037 mmol) in toluene (1 ml) was treated with 50% aqueous TFA (0.3 ml), the mixture was stirred at 50 °C for 4 h, concentrated, and the residue extracted with CH_2Cl_2 (3 x 15 ml). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (1 x 2 ml), brine (1 x 2 ml), dried ($MgSO_4$), filtered, and evaporated. Flash column chromatography (CH_2Cl_2/MeOH/aqueous NH_3 92:8:1) afforded a mixture of alcohols **218** (3 mg, 22% from **217**). R_f (AcOEt/MeOH 5:1) 0.33; IR ($CHCl_3$): n 3606 (w), 3386 (w), 3021 (w), 3006 (w), 2934 (w), 1799 (w), 1730 (w), 1686 (m), 1631 (s), 1508 (m), 1453 (m), 1439 (m), 1413 (m), 1363 (w), 1283 (m), 1265 (m), 1159 (w), 1092 (w), 1035 (m), 908 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz, 1:1 mixture of 2 diastereoisomers): δ 7.13 (dd, J = 10.8, 3.0 Hz, 0.5H), 7.07 (dd, J = 10.2, 4.2 Hz, 0.5H), 7.01 (dd, J = 10.4, 4.0 Hz, 1H), 6.75-6.60 (m, 1H), 6.19 (dd, J = 10.8, 3.0 Hz, 0.5H), 6.14 (dd, J = 10.2, 1.9 Hz, 0.5H), 6.10 (dd, J = 10.4, 2.1 Hz, 1H), 4.82 (s, 1H), 4.78, 4.76 (2s, 1H), 3.88, 3.85 (2s,

3H), 3.87 (s, 3H), 3.83-3.72 (m, 2H), 3.20-2.75 (m, 12H), 2.10-2.00 (10H); LRMS-EI (*m/z*): M^+ 357 (3), 304 (13), 303 (17), 257 (22), 251 (10), 240 (14), 239 (23), 227 (19), 211 (10), 115 (10), 101 (67), 100 (61), 87 (10), 86 (81), 84 (61), 75 (25), 73 (68), 58 (30), 57 (19), 56 (13), 55 (13), 51 (11), 49 (26), 47 (31), 45 (18), 44 (100), 43 (68), 42 (24), 41 (13); HRMS-EI (*m/z*): M^+ calcd. for $C_{20}H_{23}NO_5$: 357.1576, found 357.1571.

_N_-(2-((5a*S*,6*S*,9a*R*)-1-((1,3-dioxolan-2-yl)methyl)-6-hydroxy-4-methoxy-5a,6,7,9a-tetrahydrodibenzo[*b*,*d*]furan-9a-yl)ethyl)-_N_-methyl-2,4-dinitrobenzenesulfonamide (219).

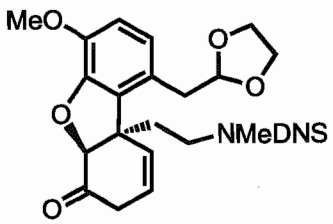


219

A solution of secondary amine **214** (61 mg, 0.17 mmol) in CH_2Cl_2 (1.5 ml) was treated with *i*Pr_2NEt (35 µl, 0.203 mmol) and dinitrobezenesulfonyl chloride (50 mg, 0.19 mmol) and stirred for 20 min. The reaction mixture treated with water (1 ml) and extracted with CH_2Cl_2 (3 x 10 ml). The combined organic layers were washed with saturated aqueous Na_2CO_3 solution and brine, dried ($MgSO_4$), filtered, and evaporated. Flash column chromatography (hexanes/AcOEt 1:1) afforded sulfonamide **219** (51 mg, 51%) as a yellow oil. R_f (hexanes/AcOEt 1:1) 0.35; $[\alpha]_D^{20}$ = +8.34° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): n 3592 (w), 3029 (w), 2983 (w), 2893 (w), 1731 (w), 1556 (s), 1541 (s), 1366 (s), 1351 (s), 1279 (m), 1165 (s), 1131 (m), 1049 (s),

946 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 8.47 (dd, *J* = 6.6., 2.2 Hz, 1H), 8.45 (d, *J* = 2.4 Hz, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 6.86 (d, *J*=8.4 Hz, 1H), 6.79 (d, *J*=8.4 Hz, 1H), 6.04 (dd, *J* = 10.1, 1.7 Hz, 1H), 5.86-5.83 (m, 1H), 5.05 (dd, *J* = 6.3, 3.5, 1H), 4.39 (d, *J* = 8.4, 1H), 4.03 (ddd, *J* = 15.5, 10.1, 7.4, 2H), 3.92-3.85 (m, 3H), 3.87 (s, 3H), 3.41-3.35 (m, 1H), 3.01 (dd, *J* = 14.5, 3.5, 1H), 2.96-2.91 (m, 1H), 2.93 (s, 3H), 2.89 (dd, *J* = 14.5, 6.4, 1H), 2.40 (dt, *J* = 17.4, 5.4, 1H), 2.16-2.11 (m, 2H), 1.99 (td, *J* = 12.1, 4.7, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ149.60, 148.05, 145.46, 144.07, 137.93, 132.58, 131.61, 128.47, 126.03, 125.72, 124.60, 124.03, 119.72, 111.80, 104.39, 90.24, 67.77, 64.99, 64.94, 55.87, 51.50, 46.38, 37.64, 36.33, 29.31; LRMS-EI (*m/z*): M^+ 591 (12), 147 (16), 136 (24), 91 (14), 89 (14), 77 (13), 73 (100); HRMS-EI (*m/z*): M^+ cald. for $C_{26}H_{29}N_3O_{11}S$: 591.1507, found 591.1522.

_N_-(2-((5a*S*,9a*R*)-1-((1,3-dioxolan-2-yl)methyl)-4-methoxy-6-oxo-5a,6,7,9a-tetrahydrodibenzo[*b*,*d*]furan-9a-yl)ethyl)-_N_-methyl-2,4-dinitrobenzenesulfonamide (220)

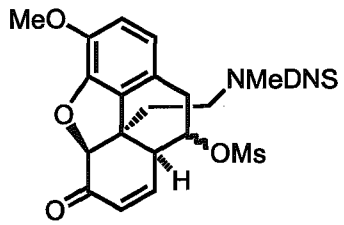


220

A suspension of alcohol **219** (64 mg, 0.11 mmol) and IBX (45 mg, 0.16 mmol) in AcOEt (3 ml) was stirred at 80 °C for 4 h, cooled to 25 °C, and filtered through Celite (washing with AcOEt) affording crude **220** (60 mg) which was used without further purification. R_f (hexanes/AcOEt 1:1) 0.23; IR ($CHCl_3$): n 3101 (w), 3032 (w), 2981

(w), 2893 (w), 1738 (m), 1556 (s), 1541 (s), 1508 (m), 1366 (s), 1351 (s), 1283 (m), 1164 (s), 1131 (m), 1044 (m), 908 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 8.49 (dd, *J* = 8.6, 1.9 Hz, 1H); 8.44 (d, *J* = 1.9 Hz, 1H), 8.15 (d, *J* = 8.6 Hz, 1H), 6.85 (d, *J*=8.4 Hz, 1H), 6.77 (d, *J*=8.4 Hz, 1H), 6.03 (d, *J* = 9.9 Hz, 1H), 5.87 (ddd, *J* = 10.0, 3.9, 3.9 Hz, 1H), 5.02 (dd, *J* = 5.6, 4.1, 1H), 4.81 (s, 1H); 4.00-3.96 (m, 2H), 3.92-3.84 (m, 2H), 3.87 (s, 3H), 3.40-3.35 (m, 1H), 3.09 (ddd, *J* = 19.31, 3.86, 1.99, 1H), 3.07-3.02 (m, 2H), 2.96-2.93 (m, 1H), 2.94 (s, 3H), 2.30-2.22 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 203.68, 149.70, 148.09, 146.74, 143.84, 137.65, 132.65, 129.82, 128.73, 126.17, 124.71, 124.53, 124.12, 119.77, 112.67, 104.37, 87.68, 64.99, 64.97, 57.38, 56.17, 46.37, 37.30, 36.86, 36.14, 35.05; LRMS-EI (*m/z*): M^+ 591 (12), 147 (16), 136 (24), 91 (14), 89 (14), 77 (13), 73 (100); HRMS-EI (*m/z*): M^+ calcd. for $C_{26}H_{29}N_3O_{11}S$: 591.1507, found 591.1522.

(2a²*R*,6a*S*,9a*S*)-5-Methoxy-2a²-(2-(N-methyl-2,4-dinitrophenylsulfonamido)ethyl)-7-oxo-1,2,2a²,6a,7,9a-hexahydrophenanthro[4,5-bcd]furan-1-yl methanesulfonate (221).



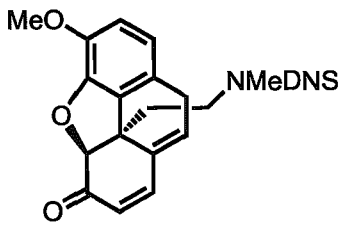
221

A solution of crude **220** (15 mg, 0.025 mmol) in toluene (1 ml) was treated with 50% aqueous TFA (0.14 ml) and the biphasic mixture was stirred at 50 °C for 2 h. The volatiles were removed in vacuo, the residue was dissolved in CH_2Cl_2 (1 ml) and

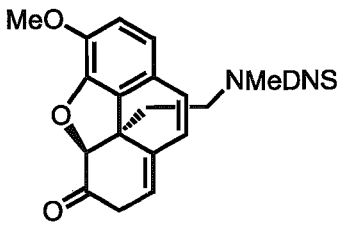
treated with *i*Pr_2NEt (5.0 µl, 0.038 mmol) and MsCl (2.4 µl, 0.031 mmol) at 0 °C. The mixture was stirred for 30 min at 0 °C, treated with saturated aqueous NH_4Cl solution (1 ml) and extracted with CH_2Cl (3 x 5 ml). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated. Flash column chromatography ($CHCl_3$/EtOAc 3:1) afforded **221** (1 mg, 6 %). The ^1H NMR spectrum was identical to one reported in the literature.[97]

R_f (hexanes/AcOEt 1:3) 0.51; ^1H NMR ($CDCl_3$, 600 MHz): δ 8.49-8.44 (m, *2*H); 8.08 (d, *J* = 8.4 Hz, 1H), 6.90 (dd, *J* = 10.3, 4.0 Hz, 1H), 6.77 (d, *J*=8.6 Hz, 1H), 6.73 (d, *J*=8.6 Hz, 1H), 6.20 (dd, *J* = 10.6, 2.3 Hz, 1H), 4.86 (s, 1H), 3.88 (s, 3H), 3.51-3.43 (m, 1H), 3.23-3.18 (m, 1H), 3.16 (s, 3H), 3.16 (s, 1H), 3.12-3.09 (m, 1H), 2.94 (s, 3H), 2.89-2.87 (m, 1H), 2.26-2.18 (m, 2H).

_N_-(2-((2a^1_R_, 5a_S_)-7-Methoxy-5-oxo-1,2a1,5,5a-tetrahydrophenanthro[4,5-bcd]furan-2a1-yl)ethyl)-N-methyl-2,4-dinitrobenzenesulfonamide (222) and **_N_-(2-((2a^1_R_, 5a_S_)-7-methoxy-5-oxo-2a1,4,5,5a-tetrahydrophenanthro[4,5-bcd]furan-2a1-yl)ethyl)-_N_-methyl-2,4-dinitrobenzenesulfonamide (223).**



222



223

A solution of crude **220** (10 mg) in toluene (1 ml) was treated with 50% aqueous TFA (0.1 ml), and the biphasic mixture was stirred at 50 °C for 2 h. The volatiles were removed in vacuo, the residue was dissolved in CH_2Cl_2 (1 ml), cooled to 0 °C,

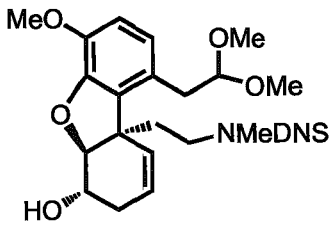
treated with *i*Pr_2NEt (12 µl, 0.085 mmol) and MsCl (5.0 µl, 0.077 mmol), and stirred for 30 min. The reaction mixture was treated with saturated aqueous NH_4Cl solution (1 ml) and extracted with CH_2Cl_2 (3 x 5 ml). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated. Flash column chromatography ($CHCl_3$/AcOEt 3:1) afforded **222** (3 mg, 33% from **219**) and a mixture of **222/223** ≈ 1:1.5 (2 mg, 22% from **219**).

Data for **222**: R_f ($CHCl_3$/AcOEt 2:1) 0.47; IR ($CHCl_3$): n 3101 (w), 3026 (w), 3012 (w), 2961 (w), 2930 (w), 1784 (w), 1730 (m), 1686 (m), 1641(w), 1604 (w), 1556 (s), 1541 (s), 1506 (m), 1455 (w), 1440 (w), 1367 (s), 1350 (s), 1265 (m), 1235 (m), 1162 (s), 1102 (s), 1046 (m), 1008 (m), 963 (w), 950 (w), 905 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 8.47-8.43 (m, 1H), 8.07 (d, *J* = 7.9 Hz, 1H), 7.26 (1H overlapped with a signal of residual $CHCl_3$), 6.75 (d, *J* = 7.9 Hz, 1H), 6.71 (d, *J* = 7.9 Hz, 1H), 6.40 (d, *J* = 7.2 Hz, 1H), 5.98 (d, *J* = 10.2 Hz, 1H), 4.99 (s, 1H), 3.87 (s, 3H), 3.59 (d, *J* = 20.0 Hz, 1H), 3.46-3.38 (m, 2H), 3.14-3.07 (m, 1H), 2.91 (s, 3H), 2.19 (td, *J* ≈ 12.1, 4.9 Hz, 1H), 2.11 (td, *J* ≈ 12.1, 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 193.43, 149.89, 148.26, 145.34, 143.24, 139.20, 137.70, 131.26, 126.36, 143.96, 133.51, 131.26, 126.22, 120.51, 119.93, 113.95, 125.28, 86.86, 56.84, 47.91, 46.70, 37.67, 35.28, 30.65; LRMS-EI (*m/z*): M^+ 527 (9), 266 (32), 252 (22), 251 (56), 250 (21), 240 (65), 239 (55), 238 (62), 235 (26), 231 (21), 225 (54), 223 (54), 211 (25), 168 (44), 152 (24), 139 (41), 76 (42), 75 (50), 74 (27), 64 (100), 63 (34), 51 (42), 45 (44), 44 (85); HRMS-EI (*m/z*): M^+ calcd. for $C_{24}H_{21}N_3O_9S$: 527.0998, found 527.1018.

Data for **223**: R_f ($CHCl_3$/AcOEt 2:1) 0.53; ^1H NMR ($CDCl_3$, 600 MHz, mixture of **222/223** ≈ 1:1.3): δ 8.50-8.43 (m, overlapped with signals of **222**, 2H), 8.14 (d, *J* =

9.1 Hz, 1H), 6.74 (d, J = 9.1 Hz, 1H), 6.69 (d, J = 9.1 Hz, 1H), 6.45 (d, J = 9.1 Hz, 1H), 6.17 (d, J = 9.1 Hz, 1H), 5.77 (d, J = 7.2 Hz, 1H), 5.28 (s, 1H), 3.91 (s, 3H), 3.48-3.36 (m, overlapped with signals of **222**, 2H), 3.30-3.20 (m, 1H); 2.92 (dd, J = 16.2, 7.2 Hz, partially overlapped with a signal of MeN of **222**, 1H), 2.89 (s, 3H), 2.22-2.07 (m, overlapped with signals of **222**, 2H).

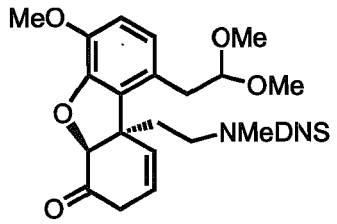
_N_-(2-((5a_S_,6_S_,9a_R_)-1-(2,2-Dimethoxyethyl)-4-methoxy-6-oxo-5a,6,7,9a-tetrahydrodibenzo[_b_,_d_]furan-9a-yl)ethyl)-_N_-methyl-2,4-dinitrobenzenesulfonamide (224).



224

A solution of **219** (42 mg, 0.071 mmol) and *p*TsOH (6 mg, 0.04 mmol) in MeOH was refluxed for 3 d, cooled to 25 °C, treated with with saturated aqueous Na_2CO_3 solution (2 ml), and extracted with CH_2Cl_2 (3 x 10 ml). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated. Flash column chromatography (hexanes/AcOEt 1:3) afforded dimethyl acetal **224** (36 mg, 86 %) as a yellow oil whose ^1H NMR spectrum was identical to that of its enantiomer reported in the literature.[97]

***N*-(2-((5a*S*,9a*R*)-1-(2,2-Dimethoxyethyl)-4-methoxy-6-oxo-5a,6,7,9a-tetrahydrodibenzo[*b*,*d*]furan-9a-yl)ethyl)-*N*-methyl-2,4-dinitrobenzenesulfonamide (225).**

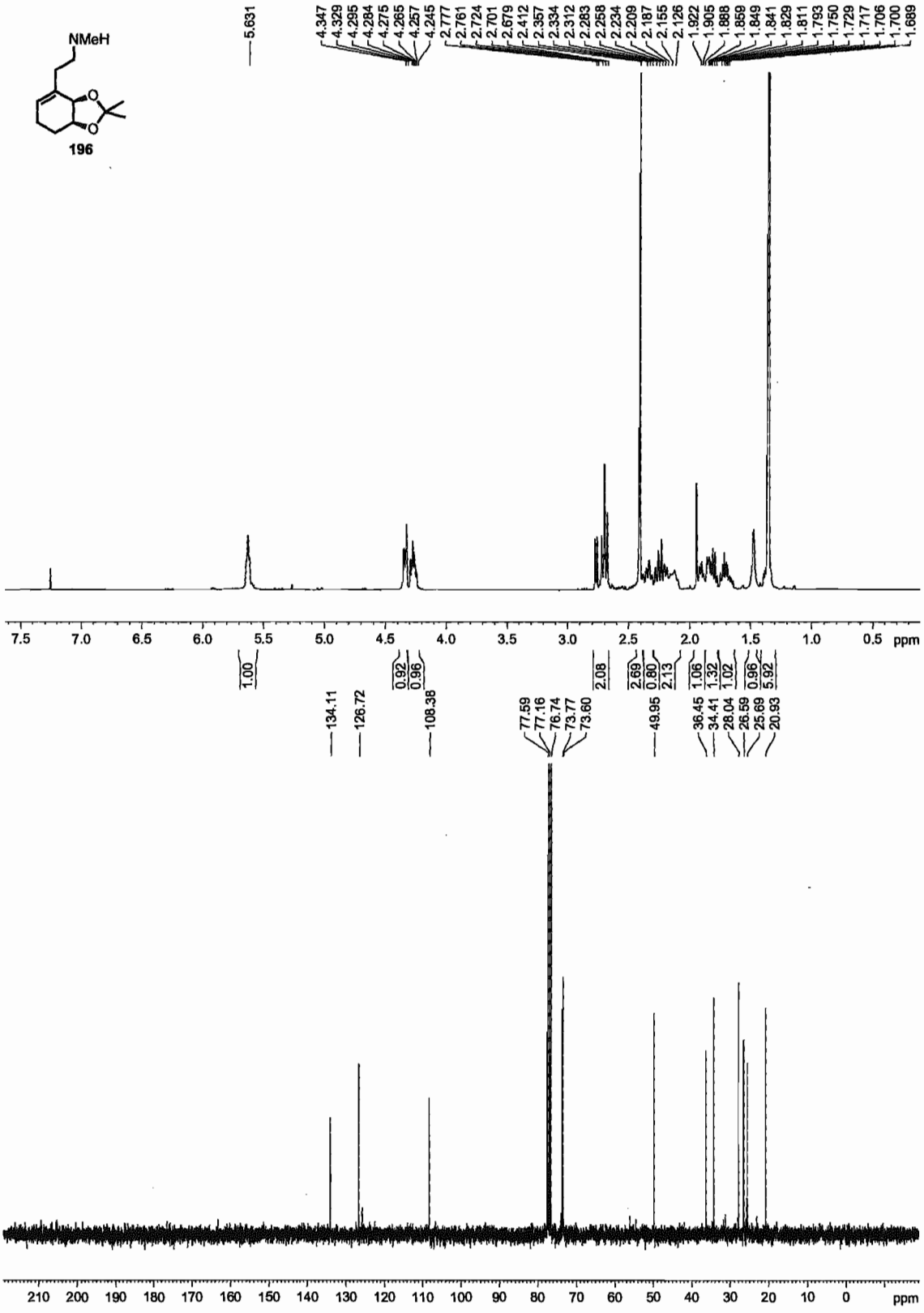


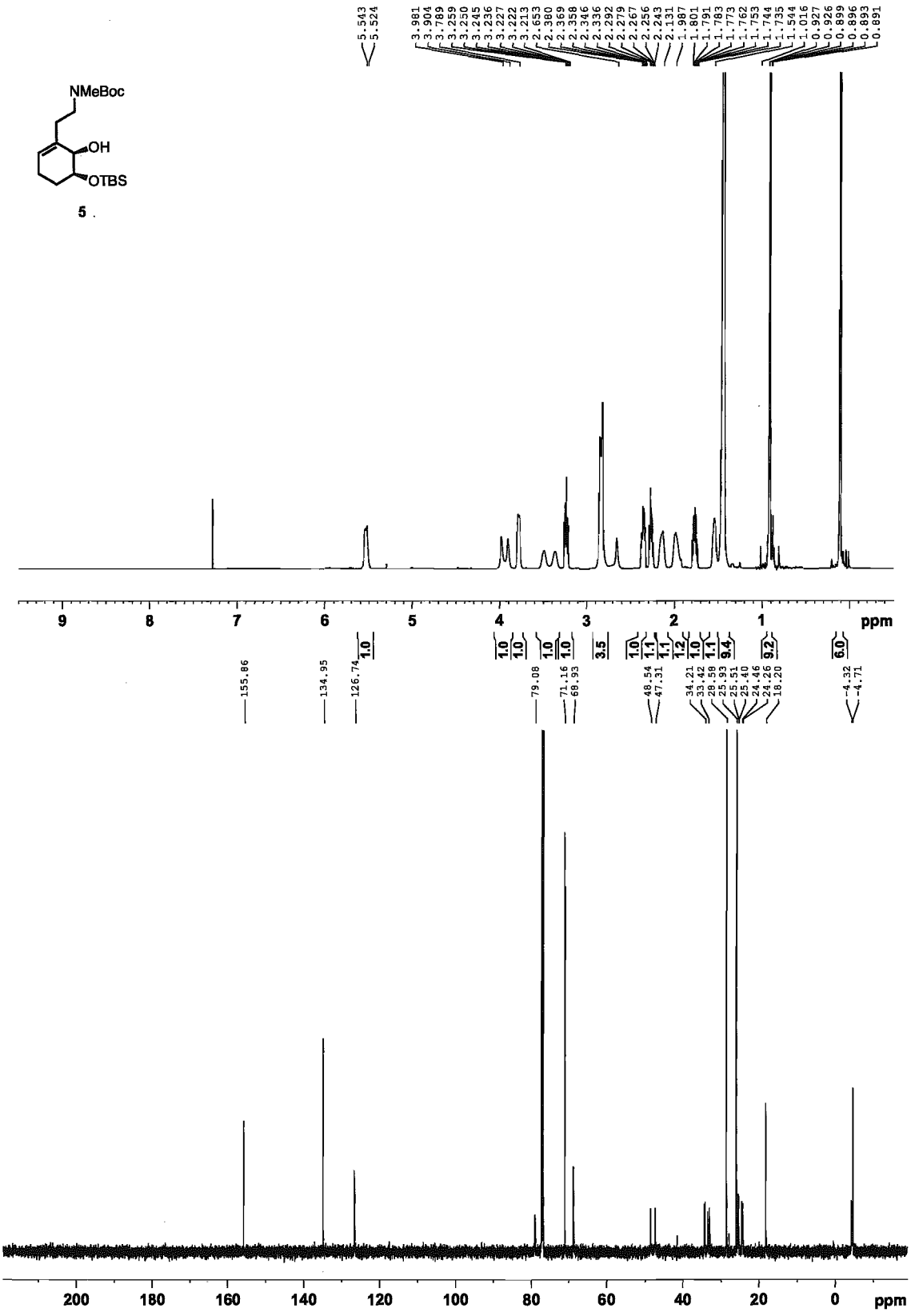
225

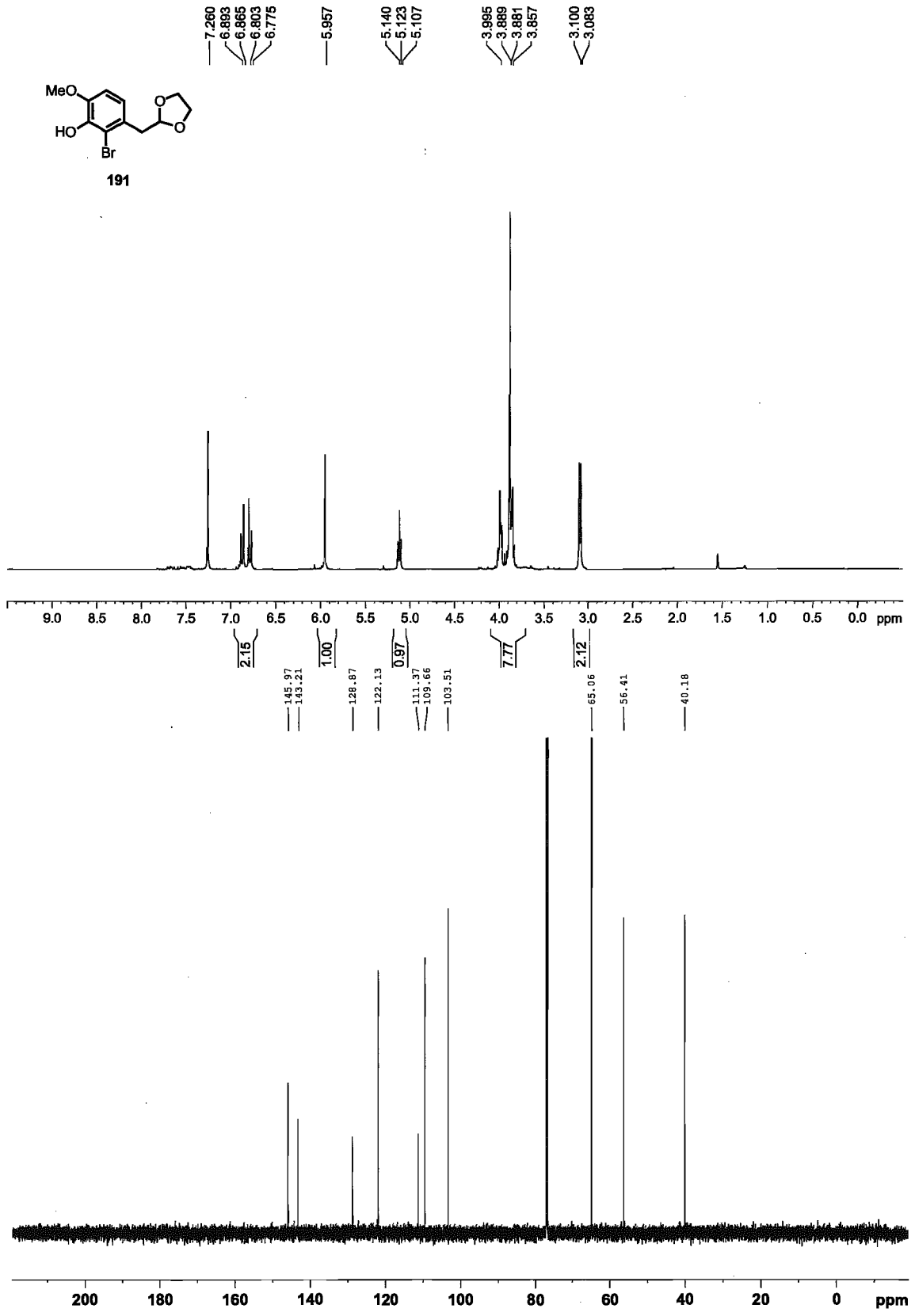
A suspension of dimethyl acetal **224** (36 mg, 0.061 mmol) and IBX (25 mg, 0.91 mmol) in AcOEt (2 ml) was stirred at 80 °C for 3 h. The reaction mixture was cooled to 25 °C and filtered through Celite (washing with AcOEt) affording crude ketone **225** (33 mg, 91 %) as a yellow oil which was used in the next step without further purification. R_f (hexanes/AcOEt 1:1) 0.35; $[\alpha]_D^{20}$ = +25.5° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 2982 (w), 2936 (w), 1731 (s), 1556 (m), 1541 (m), 1507 (w), 1374 (m), 1351 (m), 1267 (m), 1164 (m), 1046 (s), 908 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.49 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.44 (d, *J* = 2.0 Hz, 1H), 8.14 (d, *J* = 8.6 Hz, 1H), 6.79 (d, *J*=8.6 Hz, 1H), 6.76 (d, *J*=8.6 Hz, 1H), 6.03 (br d, *J* = 10.0 Hz, 1H), 5.87 (ddd, *J* = 10.0, 3.9, 3.9 Hz 1H), 4.82 (s, 1H), 4.50 (t, , *J* = 5.3 Hz, 1H), 3.88 (s, 3H), 3.35 (s, 3H), 3.32 (s, 3H), 3.34 (m, 1H), 3.17-3.01 (m, 3H); 2.94 (s, 3H); 2.86-2.83 (m, 1H); 2.27-2.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 203.85, 149.77, 146.81, 143.79, 137.75, 132.77, 129.90, 128.96, 126.29, 125.15, 124.60, 124.47, 119.90, 112.77, 105.60, 87.72, 57.59, 56.29, 54.43, 53.70, 46.50, 37.43, 36.77, 35.99, 35.14; LRMS-EI (*m/z*): M^+ 591 (1), 327 (3), 270 (9), 248 (100), 231 (55), 227 (10), 203 (19), 187 (5), 167 (25), 163 (7) 149 (72), 128

(69), 127 (51), 122 (38.9), 105 (57); HRMS-EI (*m/z*): M^+ calcd. for $C_{26}H_{29}N_3O_{11}S$: 591.1523, found 591.1531.

6. Selected Spectra




NMeBoc
OH
OTBS
5
5.543
5.524
3.981
3.904
3.789
3.259
3.250
3.245
3.236
3.227
3.222
3.213
2.653
2.380
2.369
2.358
2.346
2.336
2.292
2.279
2.267
2.256
2.243
2.131
1.987
1.801
1.791
1.783
1.773
1.762
1.753
1.744
1.735
1.544
1.016
0.927
0.926
0.899
0.896
0.893
0.891
9 8 7 6 5 4 3 2 1 ppm
1.0 1.0 1.0 1.0 1.0 3.5 1.0 1.1 1.1 1.2 1.0 1.1 9.4 9.2 6.0
155.86
134.95
126.74
79.08
71.16
68.93
48.54
47.31
34.21
33.42
28.59
25.93
25.51
25.40
24.46
24.26
18.20
-4.32
-4.71
200 180 160 140 120 100 80 60 40 20 0 ppm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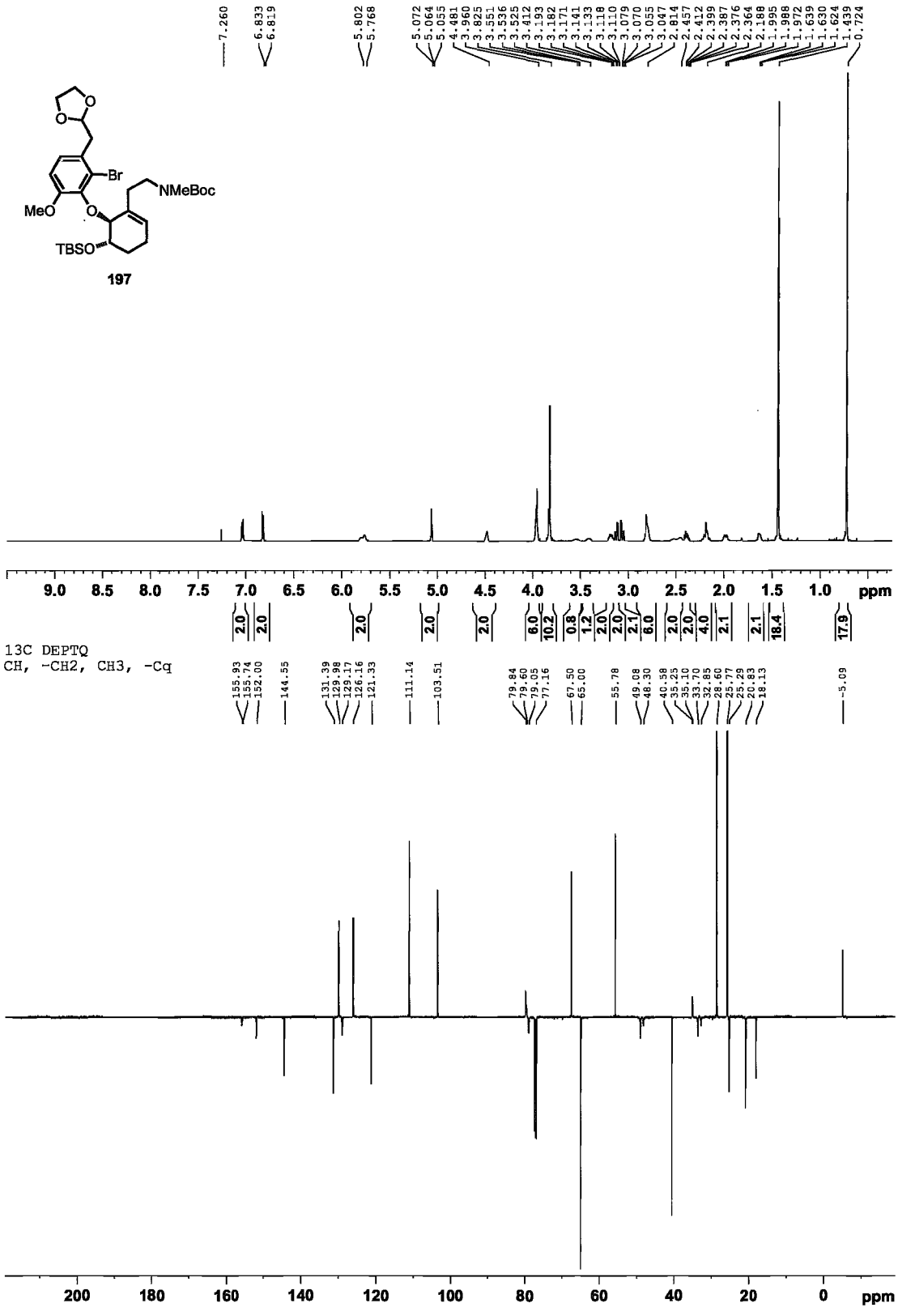
6.893
6.865
6.803
6.775
5.957
5.140
5.123
5.107
3.995
3.889
3.881
3.857
3.100
3.083
MeO
HO
Br
191
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.15
1.00
0.97
7.77
2.12
145.97
143.21
128.87
122.13
111.37
109.66
103.51
65.06
56.41
40.18
200 180 160 140 120 100 80 60 40 20 0 ppm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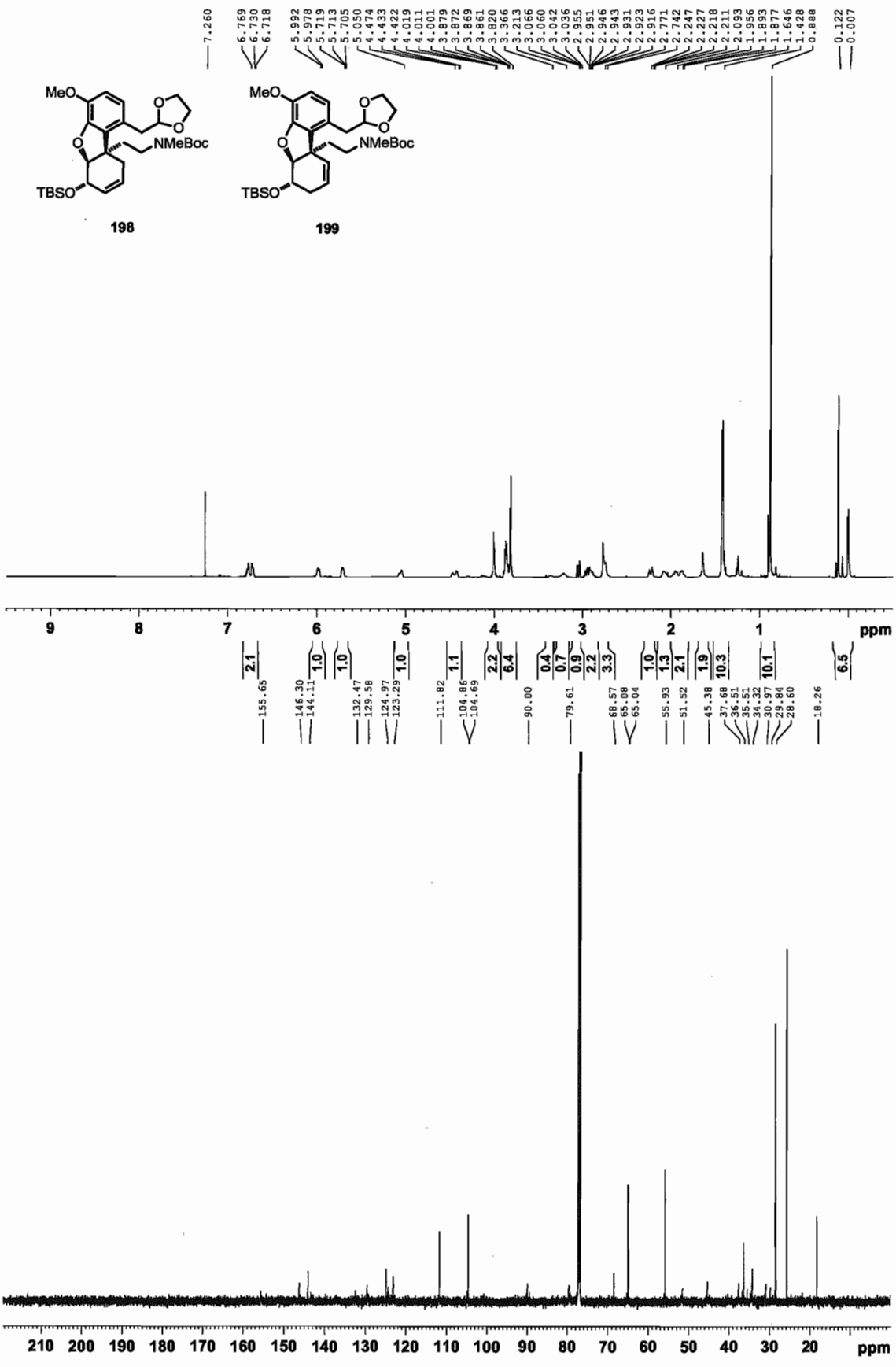
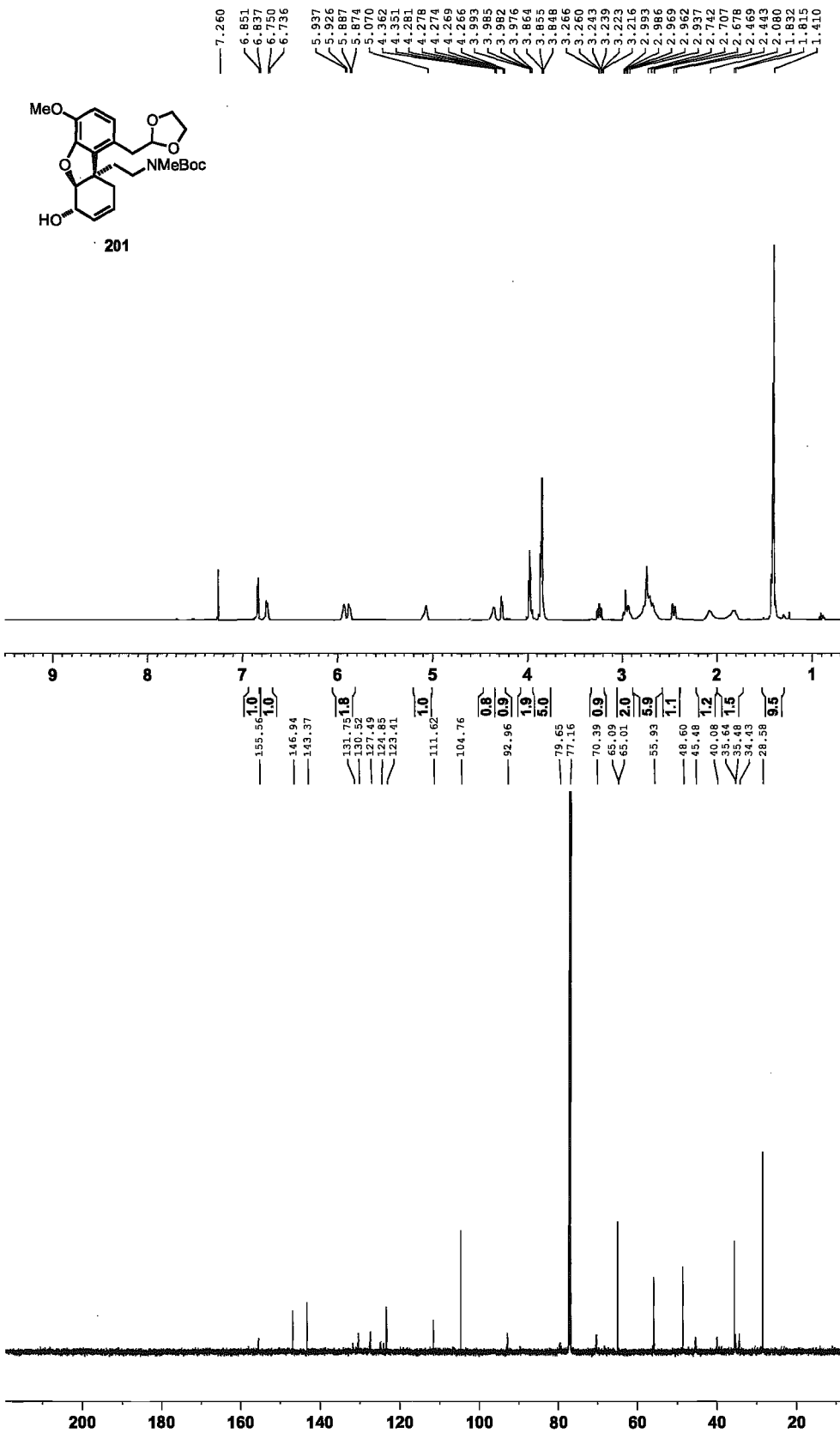
6.833
6.819
5.802
5.768
5.072
5.064
5.055
4.481
3.960
3.825
3.551
3.536
3.525
3.412
3.193
3.182
3.171
3.141
3.133
3.118
3.110
3.079
3.070
3.055
3.047
2.814
2.457
2.412
2.399
2.387
2.376
2.364
2.188
1.995
1.988
1.972
1.639
1.630
1.624
1.439
0.724
Br
NMeBoc
MeO
O
TBSO
197
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
2.0 2.0 2.0 2.0 2.0 6.0 10.2 0.8 1.2 2.0 2.0 2.1 6.0 2.0 2.0 4.0 2.1 2.1 18.4 17.9
13C DEPTQ
CH, -CH2, CH3, -Cq
155.93
155.74
152.00
144.55
131.39
129.98
129.17
126.16
121.33
111.14
103.51
79.84
79.60
79.05
77.16
67.50
65.00
55.78
49.08
48.30
40.38
35.25
35.10
33.70
32.85
28.60
25.77
25.29
20.83
18.13
-5.09
200 180 160 140 120 100 80 60 40 20 0 ppm


MeO
NMeBoc
TBSO
198
MeO
NMeBoc
TBSO
199
7.260
6.769
6.730
6.718
5.992
5.978
5.719
5.713
5.705
5.050
4.474
4.433
4.422
4.019
4.011
4.001
3.879
3.872
3.869
3.861
3.820
3.366
3.213
3.066
3.060
3.042
3.036
2.955
2.951
2.946
2.943
2.931
2.923
2.916
2.771
2.742
2.247
2.227
2.218
2.211
2.093
1.956
1.893
1.877
1.646
1.428
0.888
0.122
0.007
ppm
155.65
146.30
144.11
132.47
129.58
124.97
123.29
111.82
104.86
104.69
90.00
79.61
68.57
65.08
65.04
55.93
51.52
45.38
37.68
36.51
35.51
34.32
30.97
29.84
28.60
18.26
ppm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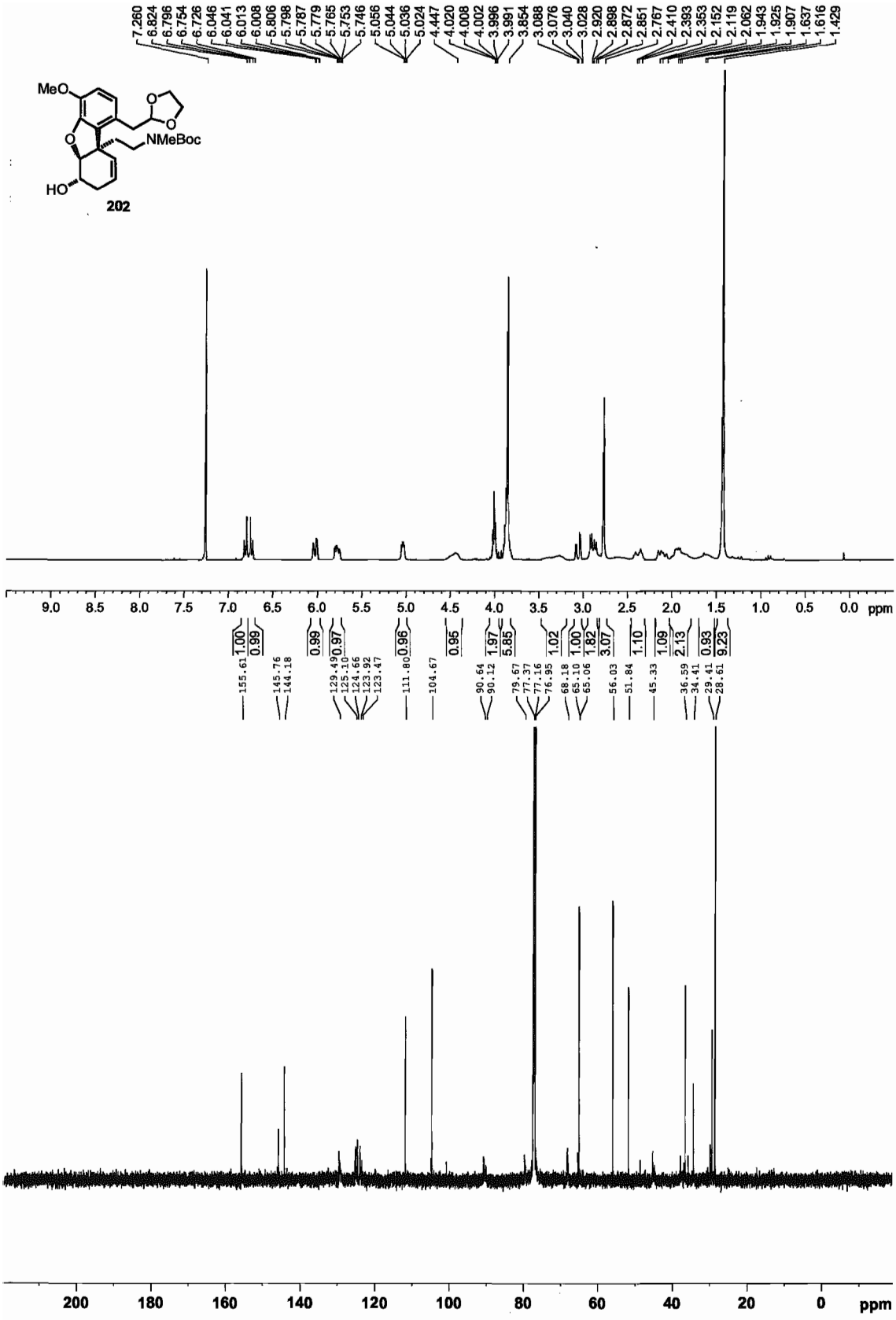
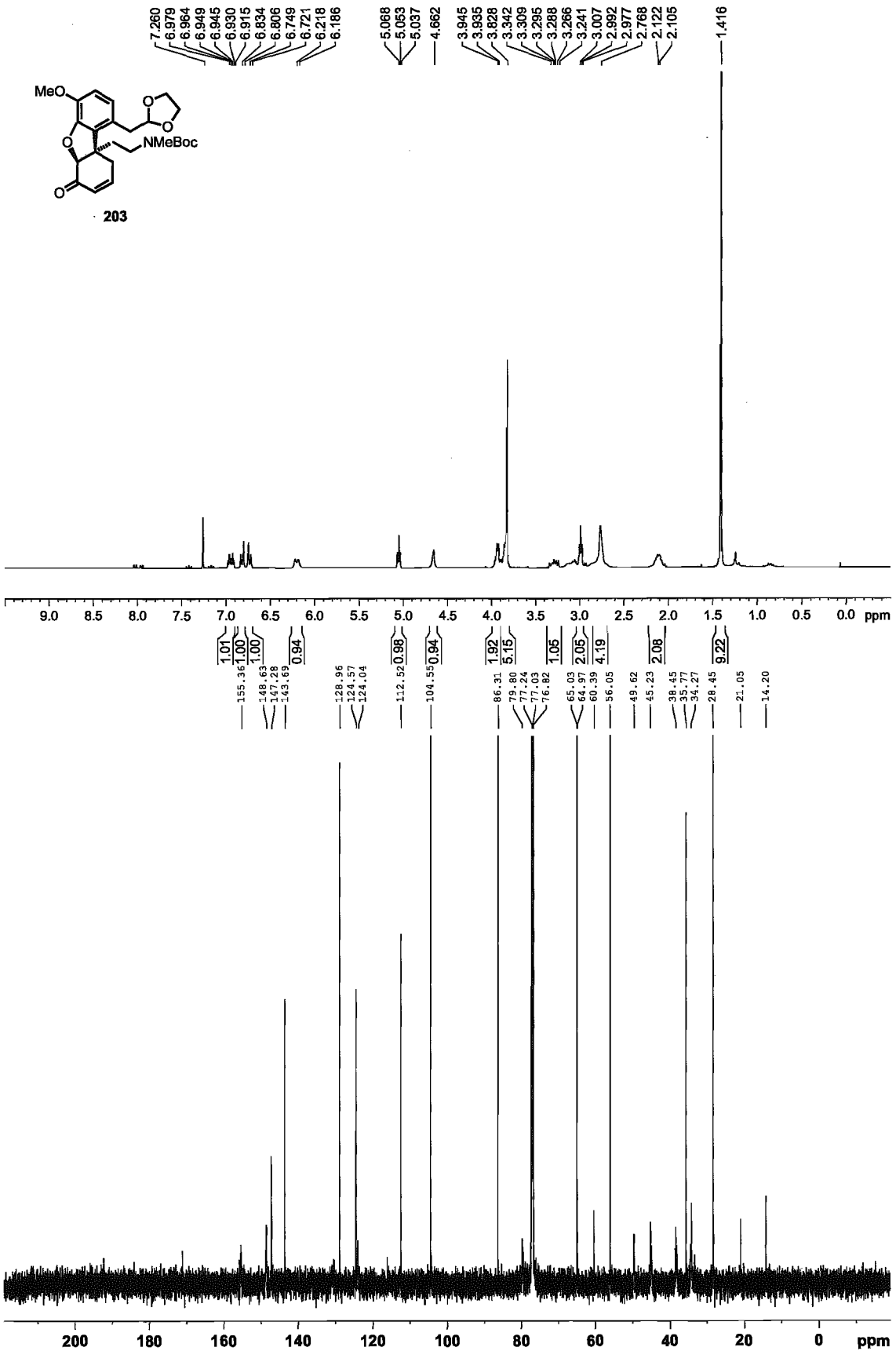
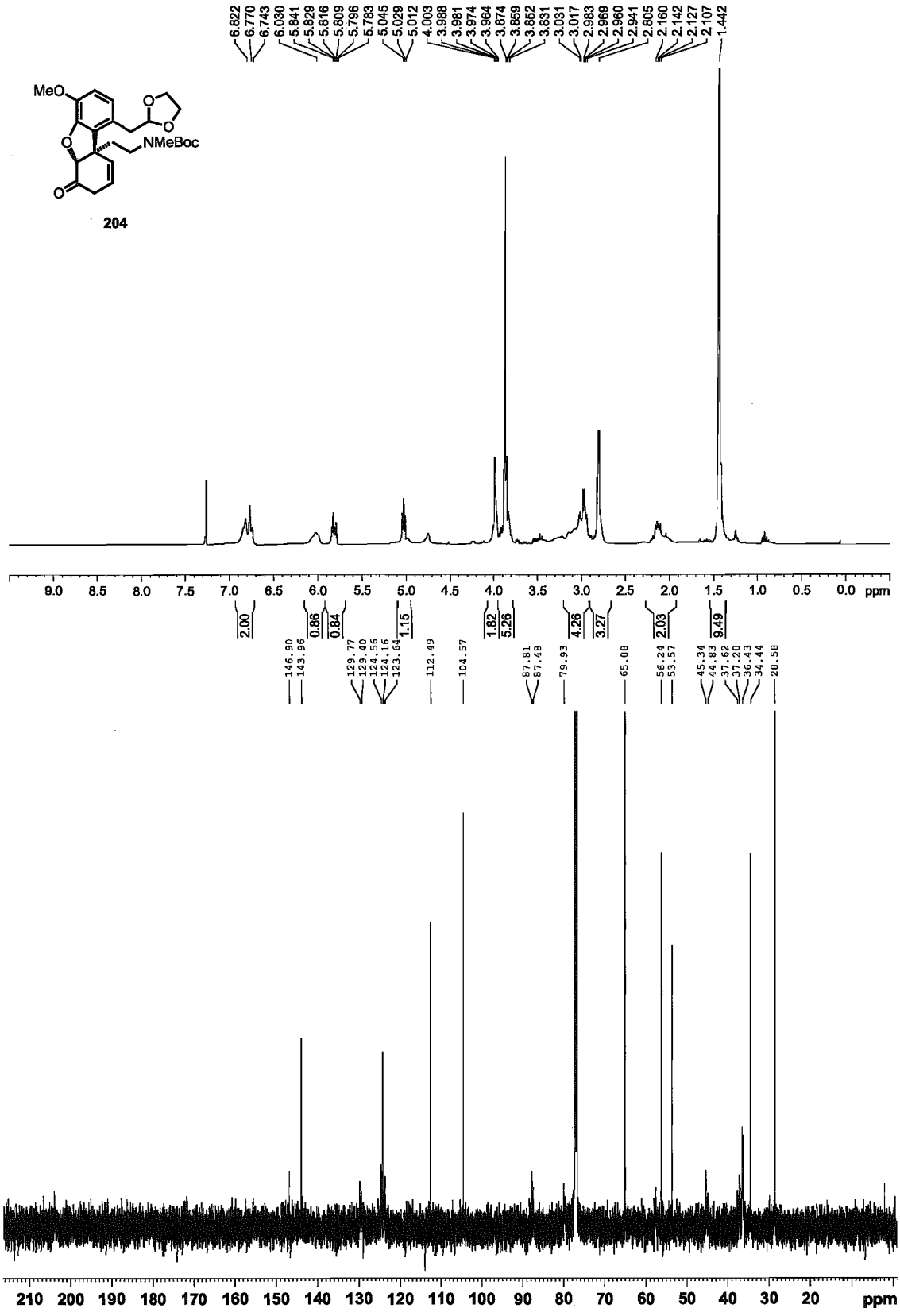
6.851
6.837
6.750
6.736
5.937
5.926
5.887
5.874
5.070
4.362
4.351
4.281
4.278
4.274
4.269
4.266
3.993
3.985
3.982
3.976
3.864
3.855
3.848
3.266
3.260
3.243
3.239
3.223
3.216
2.993
2.986
2.969
2.962
2.937
2.742
2.707
2.678
2.469
2.443
2.080
1.832
1.815
1.410
MeO
O
O
O
NMeBoc
HO
201
9
8
7
6
5
4
3
2
1
ppm
1.0
1.0
1.8
1.0
0.8
0.9
1.9
5.0
0.9
2.0
5.9
1.1
1.2
1.5
9.5
155.56
146.94
143.37
131.75
130.52
127.49
124.85
123.41
111.62
104.76
92.96
79.65
77.16
70.39
65.09
65.01
55.93
48.60
45.48
40.08
35.64
35.48
34.43
28.58
200
180
160
140
120
100
80
60
40
20
0
ppm


MeO
NMeBoc
HO
202


MeO
NMeBoc
O
O
O
O
203
7.260
6.979
6.964
6.949
6.945
6.930
6.915
6.834
6.806
6.749
6.721
6.218
6.186
5.068
5.053
5.037
4.662
3.945
3.935
3.828
3.342
3.309
3.295
3.288
3.266
3.241
3.007
2.992
2.977
2.768
2.122
2.105
1.416
ppm
155.36
148.63
147.28
143.69
128.96
124.57
124.04
112.52
104.55
86.31
79.80
77.24
77.03
76.82
65.03
64.97
60.39
56.05
49.62
45.23
38.45
35.77
34.27
28.45
21.05
14.20
ppm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NMeBoc
O
O
O
O
O
204
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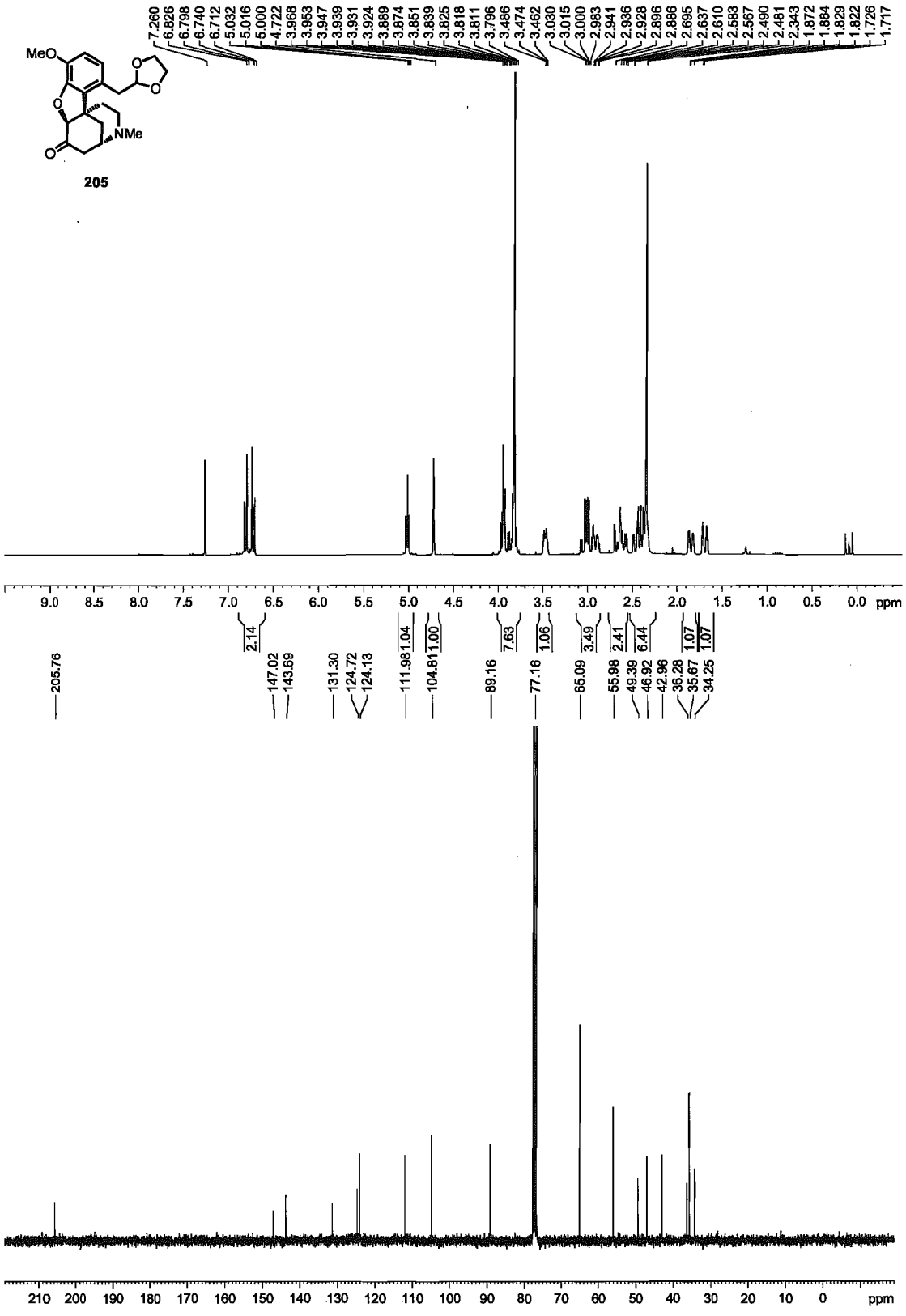
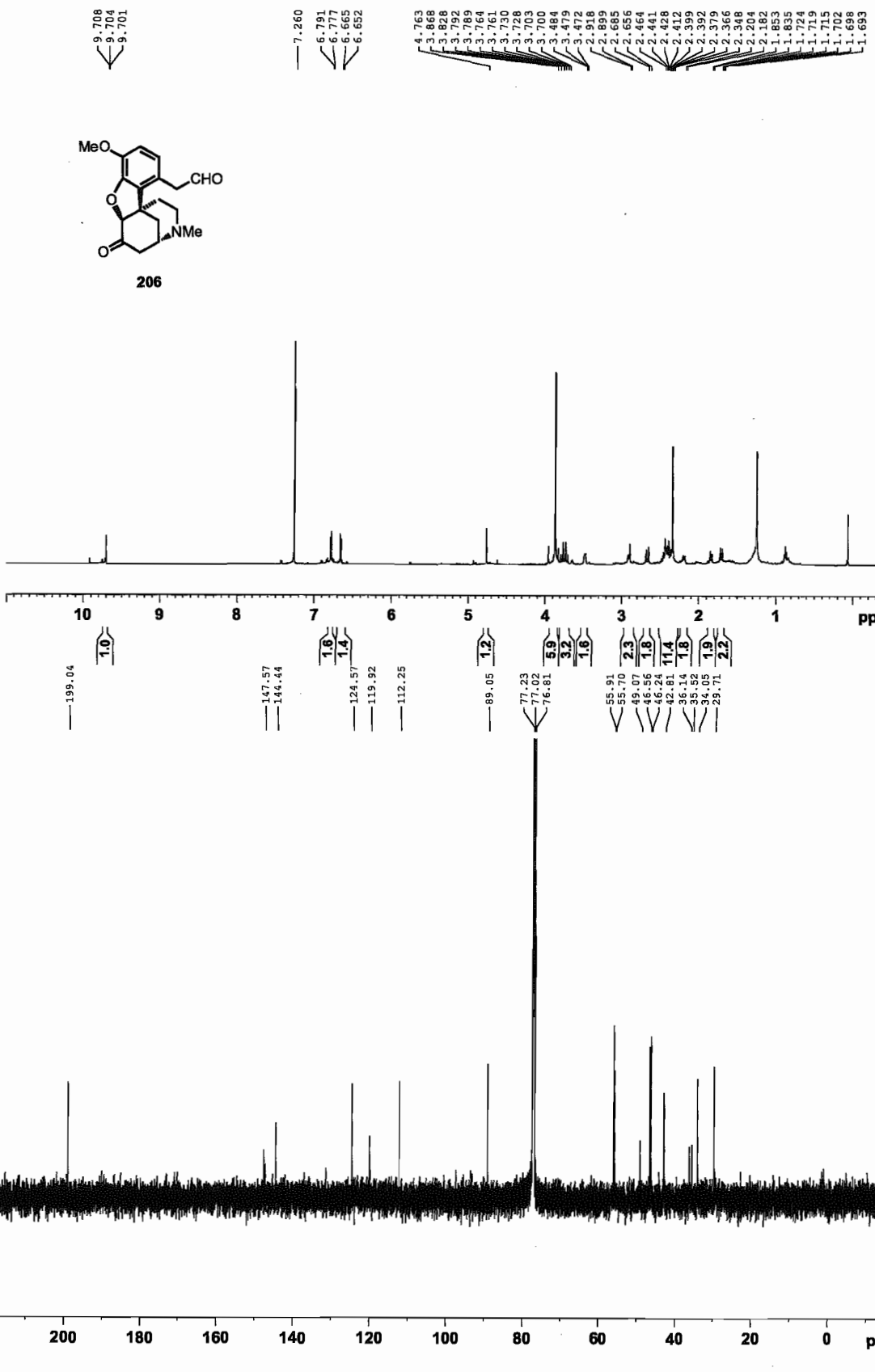
6.770
6.743
6.030
5.841
5.829
5.816
5.809
5.796
5.783
5.045
5.029
5.012
4.003
3.988
3.981
3.974
3.964
3.874
3.859
3.852
3.831
3.031
3.017
2.983
2.969
2.960
2.941
2.805
2.160
2.142
2.127
2.107
1.442
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.00
0.86
0.84
1.15
1.82
5.26
4.26
3.27
2.03
9.49
146.90
143.96
129.77
129.40
124.56
124.16
123.64
112.49
104.57
87.81
87.48
79.93
65.08
56.24
53.57
45.34
44.83
37.62
37.20
36.43
34.44
28.58
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


MeO
O
O
O
NMe
O
205
7.260
6.826
6.798
6.740
6.712
5.032
5.016
5.000
4.722
3.968
3.953
3.947
3.939
3.931
3.924
3.889
3.874
3.851
3.839
3.825
3.818
3.811
3.796
3.486
3.474
3.462
3.030
3.015
3.000
2.983
2.941
2.936
2.928
2.896
2.886
2.695
2.637
2.610
2.583
2.567
2.490
2.481
2.343
1.872
1.864
1.829
1.822
1.726
1.717
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.14
1.04
1.00
7.63
1.06
3.49
2.41
6.44
1.07
1.07
205.76
147.02
143.69
131.30
124.72
124.13
111.98
104.81
89.16
77.16
65.09
55.98
49.39
46.92
42.96
36.28
35.67
34.25
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


9.708
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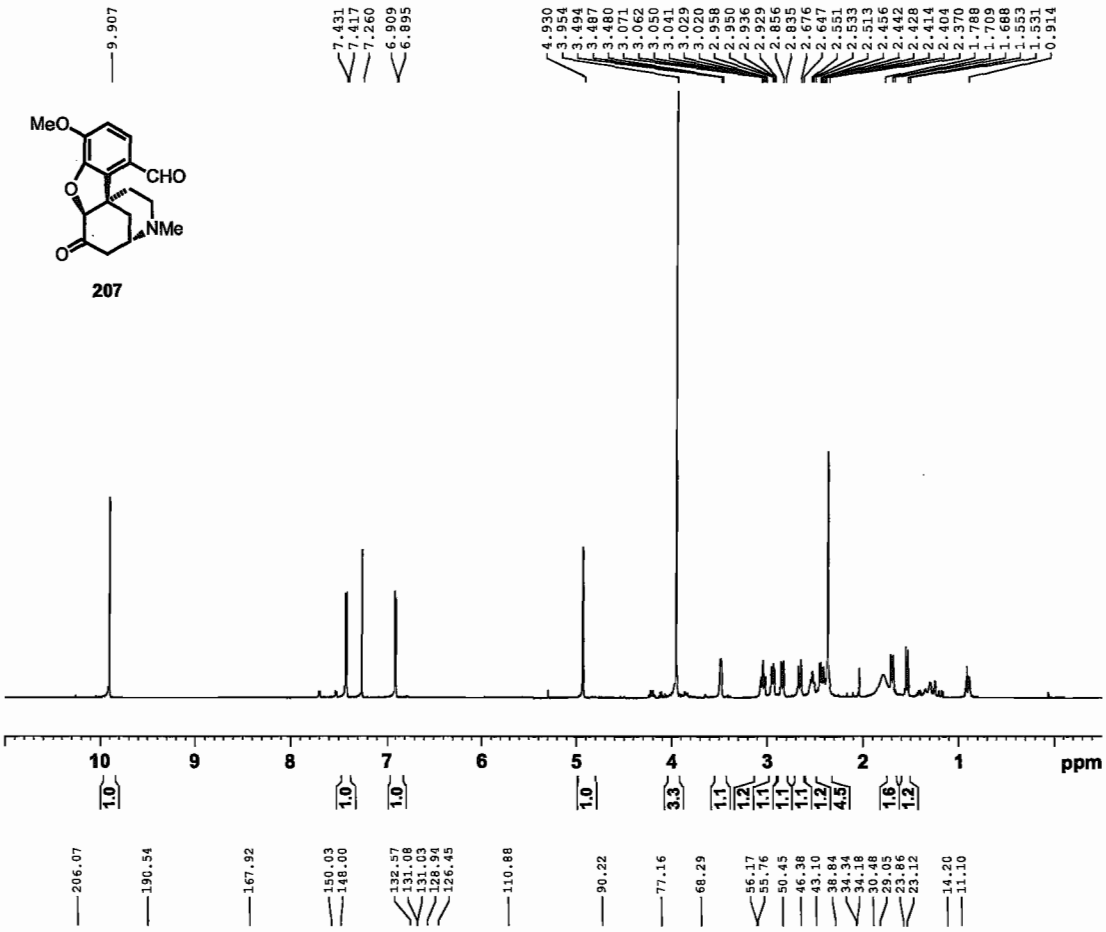
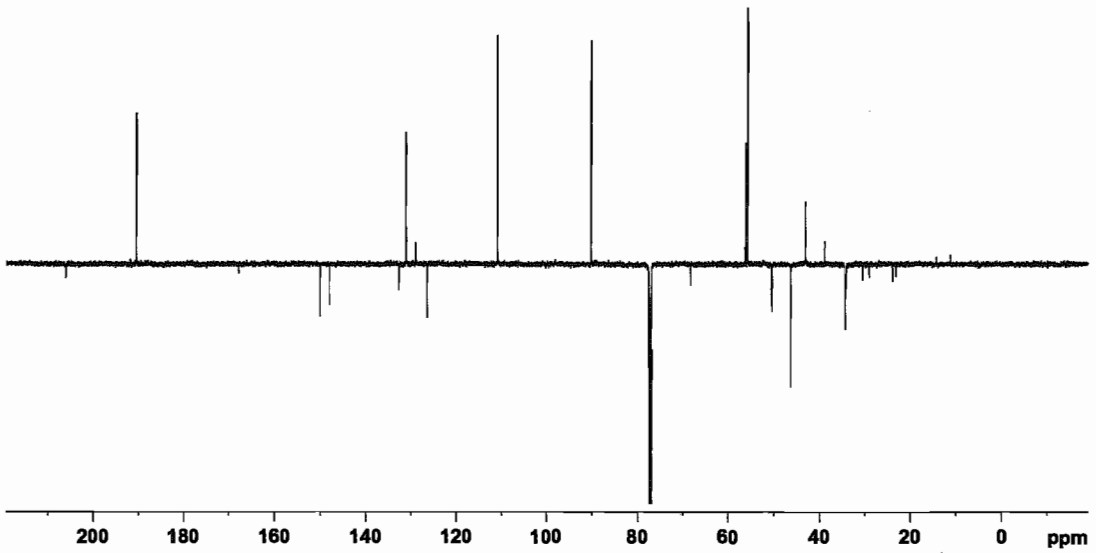
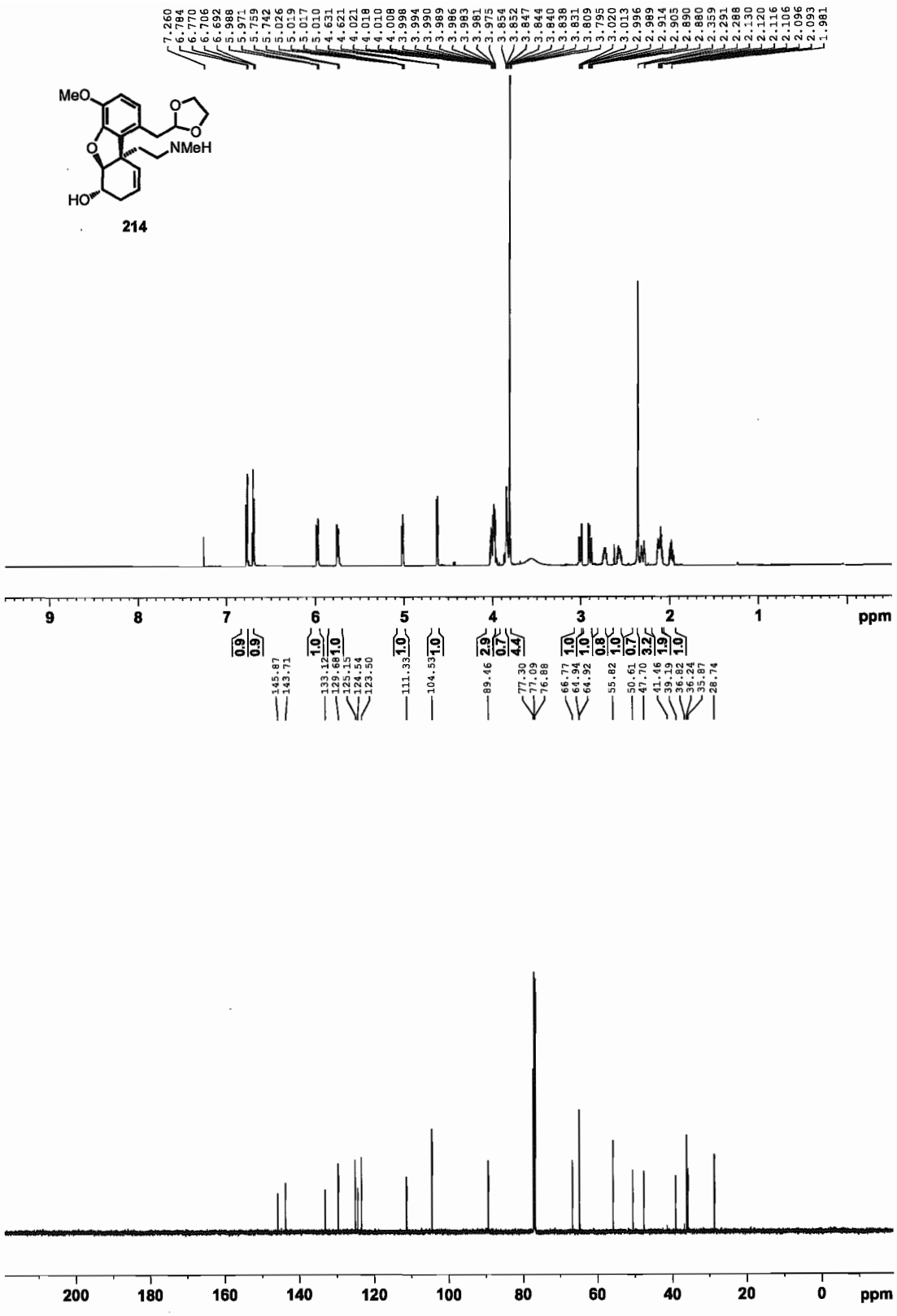
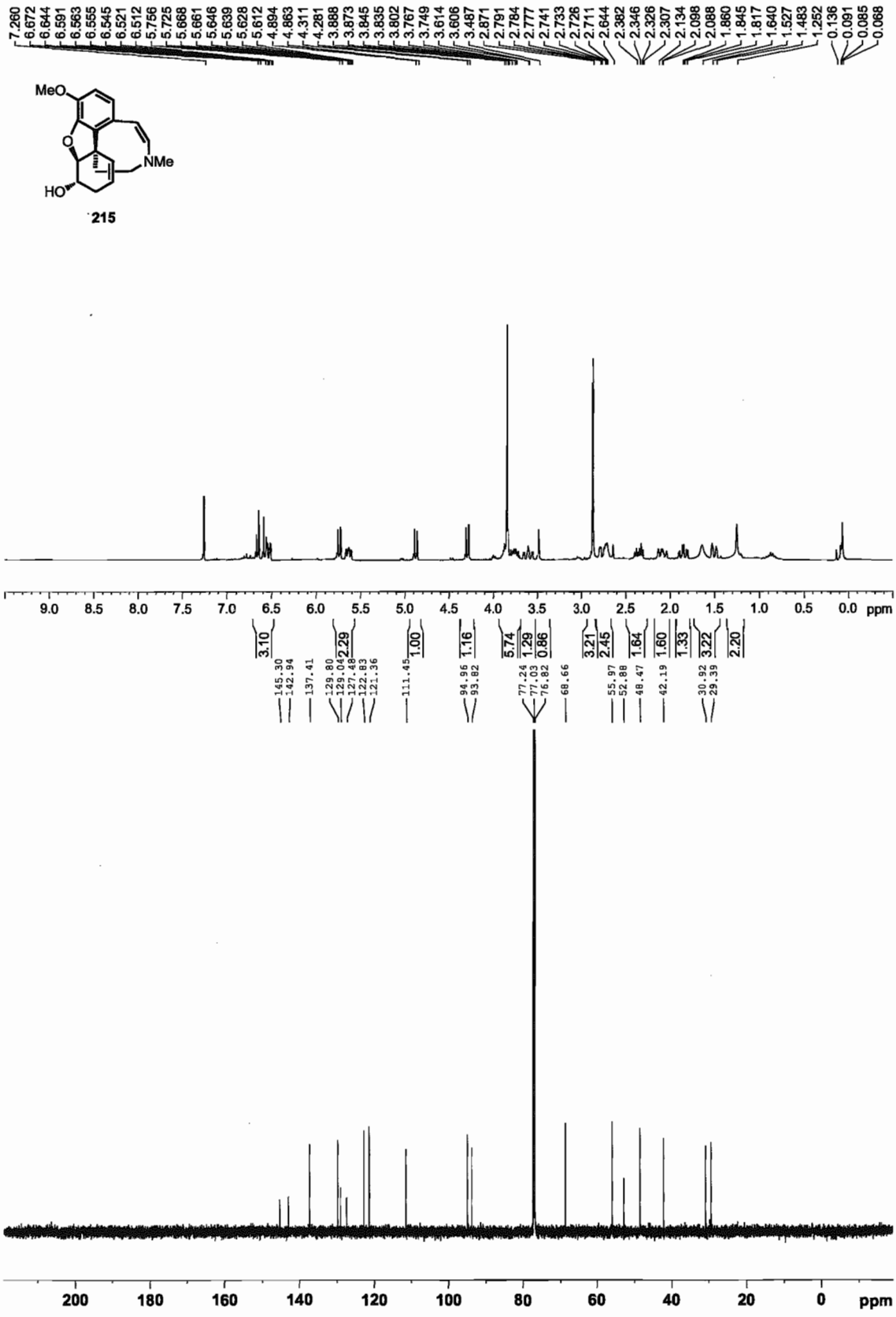
9.701
7.260
6.791
6.777
6.665
6.652
4.763
3.868
3.828
3.792
3.789
3.764
3.761
3.730
3.728
3.703
3.700
3.484
3.479
3.472
2.918
2.899
2.685
2.656
2.464
2.441
2.428
2.412
2.399
2.392
2.379
2.366
2.348
2.204
2.182
1.853
1.835
1.724
1.719
1.715
1.702
1.698
1.693
MeO
CHO
O
O
NMe
206
10
9
8
7
6
5
4
3
2
1
ppm
1.0
1.6
1.4
1.2
5.9
3.2
1.6
2.3
1.8
11.4
1.8
1.9
2.2
199.04
147.57
144.44
124.57
119.92
112.25
89.05
77.23
77.02
76.81
55.91
55.70
49.07
46.56
46.24
42.81
36.14
35.52
34.05
29.71
200
180
160
140
120
100
80
60
40
20
0
ppm



13C DEPTQ
CH, -CH2, CH3, -Cq




MeO
O
O
O
NMeH
HO
214
7.260
6.784
6.770
6.706
6.692
5.988
5.971
5.759
5.742
5.026
5.019
5.017
5.010
4.631
4.621
4.021
4.018
4.010
4.008
3.998
3.994
3.990
3.989
3.986
3.983
3.981
3.975
3.854
3.852
3.847
3.844
3.840
3.838
3.831
3.809
3.795
3.020
3.013
2.996
2.989
2.914
2.905
2.890
2.880
2.359
2.291
2.288
2.130
2.120
2.116
2.106
2.096
2.093
1.981
9
8
7
6
5
4
3
2
1
ppm
0.9
0.9
1.0
133.12
129.68
1.0
125.15
124.54
123.50
1.0
111.33
1.0
104.53
2.9
0.7
4.4
89.46
77.30
77.09
76.88
1.0
66.77
64.94
1.0
64.92
0.8
55.82
1.0
50.61
47.70
0.7
3.2
41.46
39.19
1.9
36.82
36.24
35.87
1.0
28.74
145.87
143.71
200
180
160
140
120
100
80
60
40
20
0
ppm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6.672
6.644
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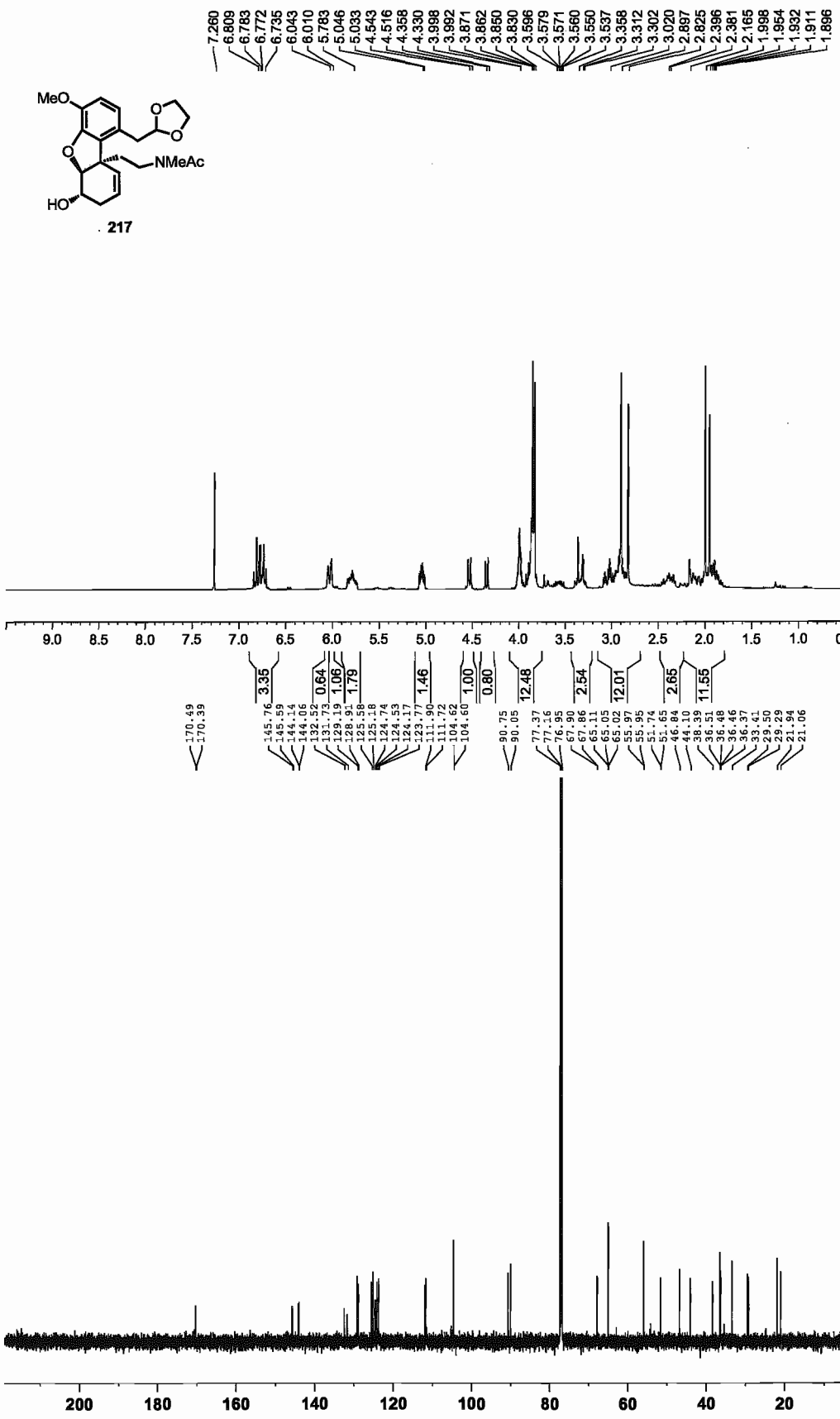
5.661
5.646
5.639
5.628
5.612
4.894
4.863
4.311
4.281
3.888
3.873
3.845
3.835
3.802
3.767
3.749
3.614
3.606
3.487
2.871
2.791
2.784
2.777
2.741
2.733
2.726
2.711
2.644
2.382
2.346
2.326
2.307
2.134
2.098
2.088
1.860
1.845
1.817
1.640
1.527
1.483
1.252
0.136
0.091
0.085
0.068
MeO
O
NMe
HO
215
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
3.10
2.29
1.00
1.16
5.74
1.29
0.86
3.21
2.45
1.64
1.60
1.33
3.22
2.20
145.30
142.94
137.41
129.80
129.04
127.48
122.83
121.36
111.45
94.96
93.82
77.24
77.03
76.82
68.66
55.97
52.88
48.47
42.19
30.92
29.39
200 180 160 140 120 100 80 60 40 20 0 ppm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5.783
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5.033
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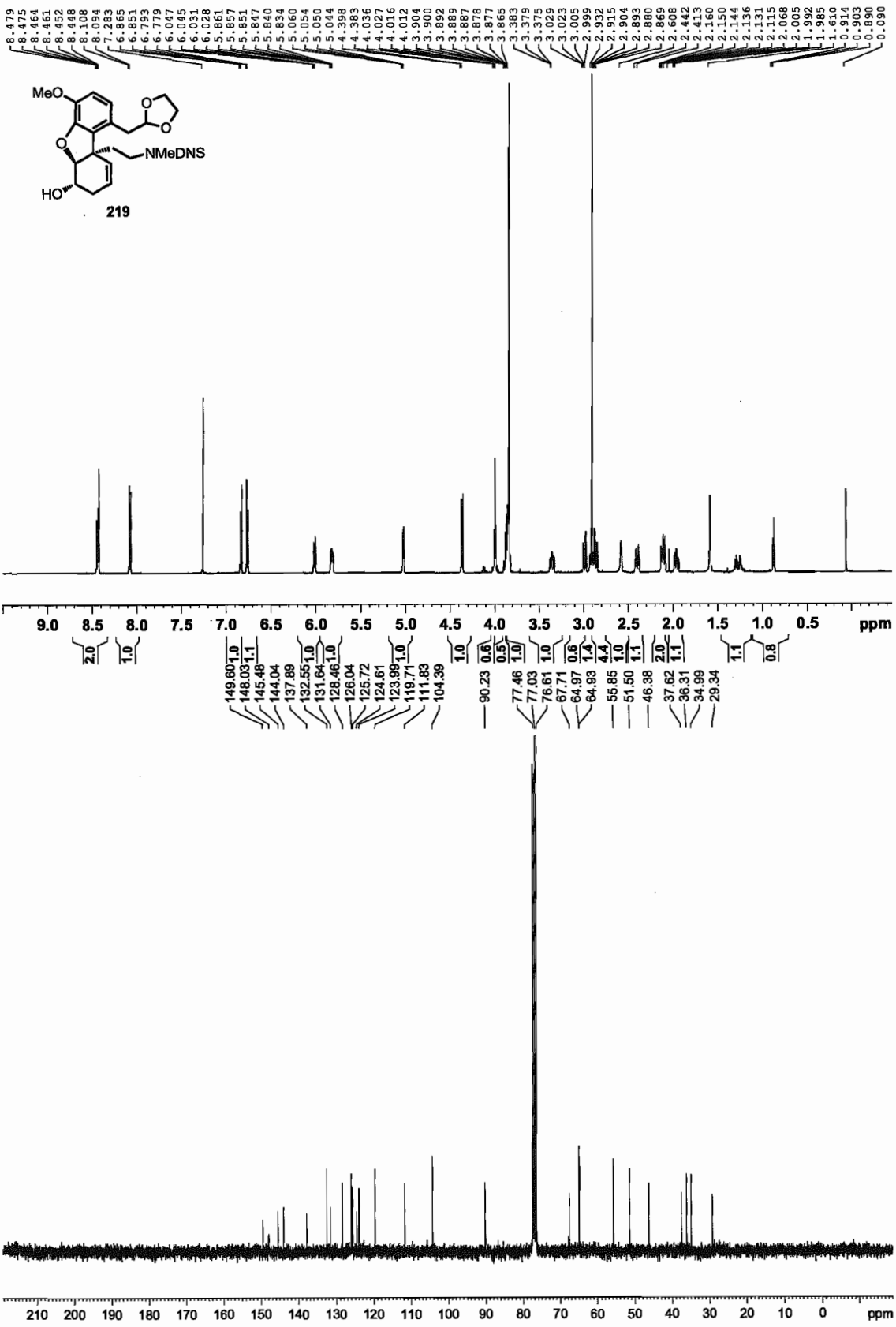
4.358
4.330
3.998
3.992
3.871
3.862
3.850
3.830
3.596
3.579
3.571
3.560
3.550
3.537
3.358
3.312
3.302
3.020
2.897
2.825
2.396
2.381
2.165
1.998
1.954
1.932
1.911
1.896
MeO
O
O
O
NMeAc
HO
217
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
3.35
0.64
1.06
1.79
1.46
1.00
0.80
12.48
2.54
12.01
2.65
11.55
170.49
170.39
145.76
145.59
144.14
144.06
132.52
131.73
129.19
128.91
125.58
125.18
124.74
124.53
124.17
123.77
111.90
111.72
104.62
104.60
90.75
90.05
77.37
77.16
76.95
67.90
67.86
65.11
65.05
65.02
55.97
55.95
51.74
51.65
46.84
44.10
38.39
36.51
36.48
36.46
36.37
33.41
29.50
29.29
21.94
21.06
200 180 160 140 120 100 80 60 40 20 0 ppm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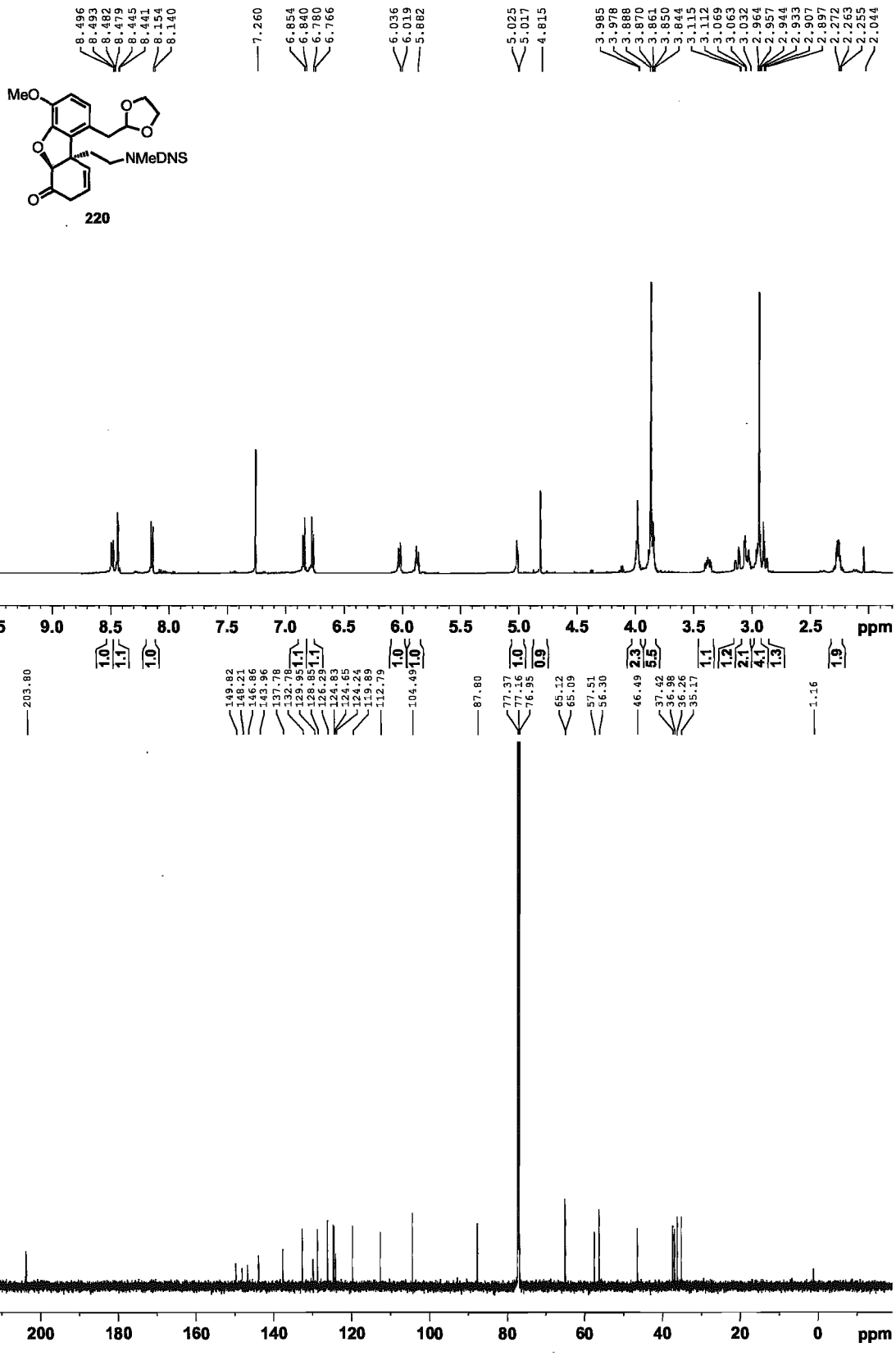
NMeDNS
HO
219
ppm
ppm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8.441
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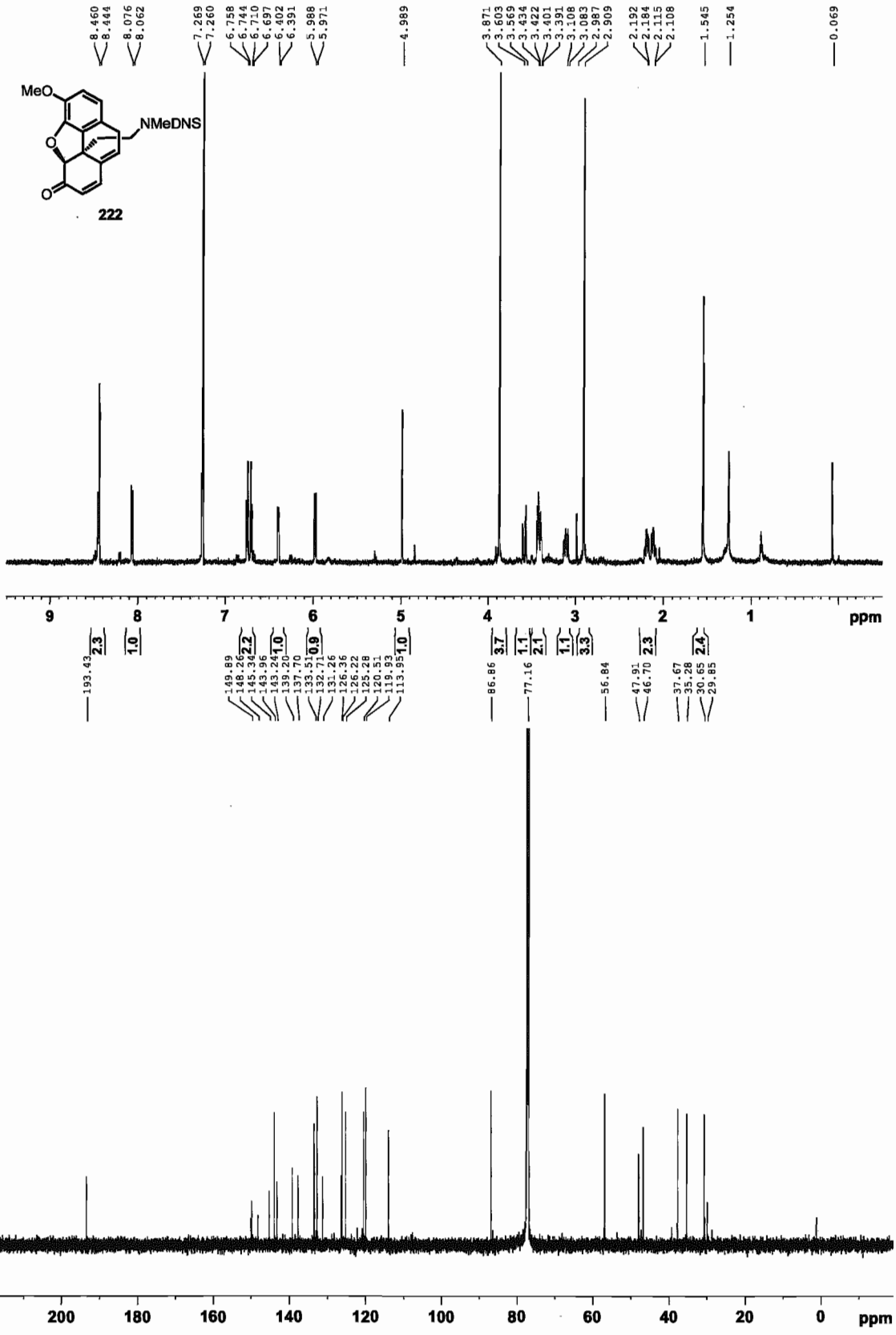
6.840
6.780
6.766
6.036
6.019
5.882
5.025
5.017
4.815
3.985
3.978
3.888
3.870
3.861
3.850
3.844
3.115
3.112
3.069
3.063
3.032
2.964
2.957
2.944
2.933
2.907
2.897
2.272
2.263
2.255
2.044
MeO
NMeDNS
220
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 ppm
1.0 1.1 1.0 1.1 1.1 1.0 1.0 1.0 0.9 2.3 5.5 1.1 1.2 2.1 4.1 1.3 1.9
203.80
149.82
148.21
146.86
143.96
137.78
132.78
129.95
128.85
126.29
124.83
124.65
124.24
119.89
112.79
104.49
87.80
77.37
77.16
76.95
65.12
65.09
57.51
56.30
46.49
37.42
36.98
36.26
35.17
1.16
200 180 160 140 120 100 80 60 40 20 0 ppm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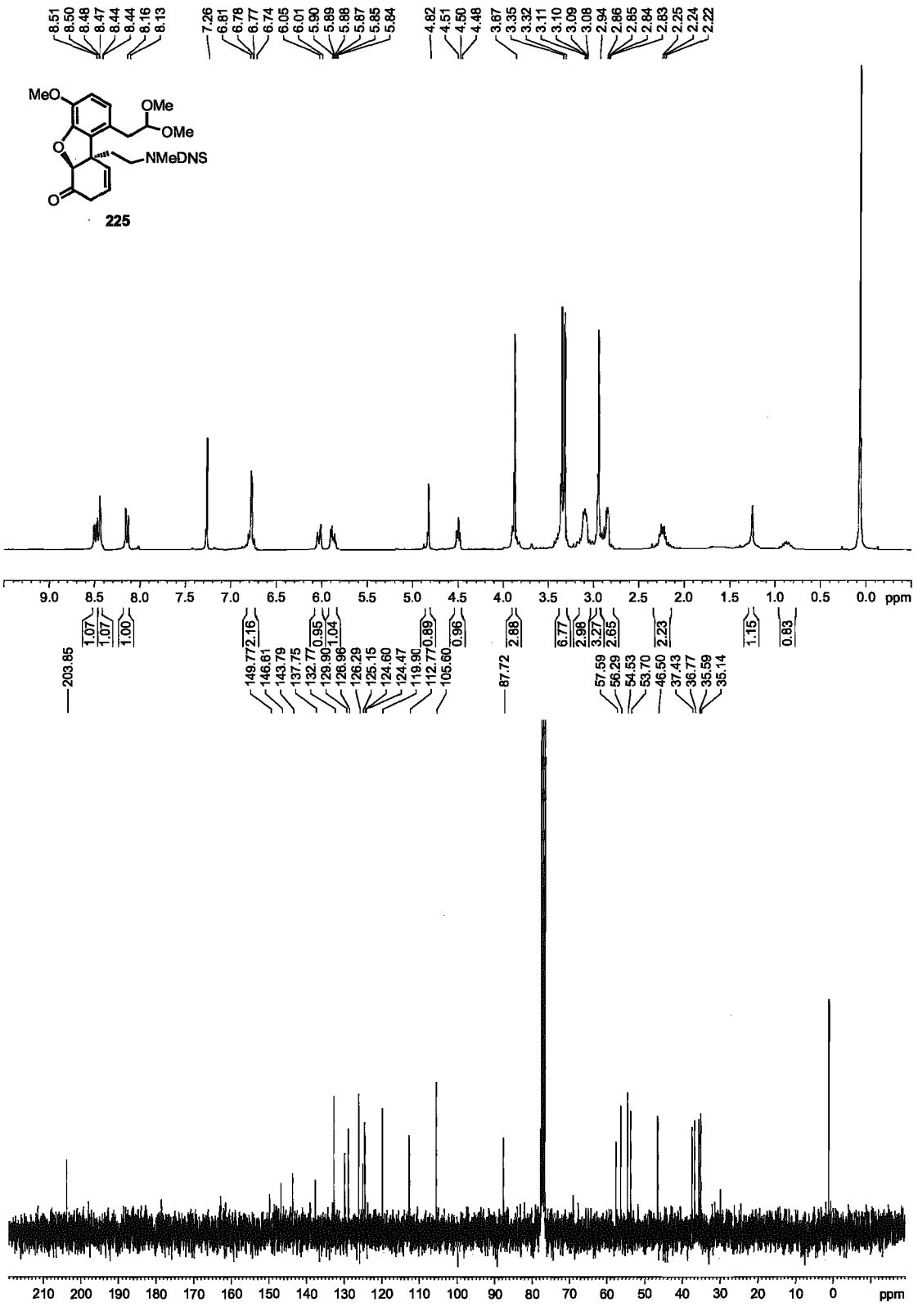
8.444
8.076
8.062
7.269
7.260
6.758
6.744
6.710
6.697
6.402
6.391
5.988
5.971
4.989
3.871
3.603
3.569
3.434
3.422
3.401
3.391
3.108
3.083
2.987
2.909
2.192
2.184
2.115
2.108
1.545
1.254
0.069
MeO
NMeDNS
O
O
222
9
8
7
6
5
4
3
2
1
ppm
2.3
1.0
2.2
1.0
0.9
1.0
3.7
1.1
2.1
1.1
3.3
2.3
2.4
193.43
149.89
148.26
145.34
143.96
143.24
139.20
137.70
133.51
132.71
131.26
126.36
126.22
125.28
120.51
119.93
113.95
86.86
77.16
56.84
47.91
46.70
37.67
35.28
30.65
29.85
200
180
160
140
120
100
80
60
40
20
0
ppm


8.51
8.50
8.48
8.47
8.44
8.44
8.16
8.13
7.26
6.81
6.78
6.77
6.74
6.05
6.01
5.90
5.89
5.88
5.87
5.85
5.84
4.82
4.51
4.50
4.48
3.67
3.35
3.32
3.11
3.10
3.09
3.08
2.94
2.86
2.85
2.84
2.83
2.25
2.24
2.22
MeO
OMe
OMe
NMeDNS
O
O
225
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.07
1.07
1.00
2.16
0.95
1.04
0.89
0.96
2.88
6.77
2.98
3.27
2.65
2.23
1.15
0.83
203.85
149.77
146.61
143.79
137.75
132.77
129.90
128.96
126.29
125.15
124.60
124.47
119.90
112.77
105.60
87.72
57.59
56.29
54.53
53.70
46.50
37.43
36.77
35.59
35.14
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

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8. Vita

Timothy Graeme Piercy was born in Cranbrook, British Columbia, Canada, on July 6th, 1982. He and his elder brother and younger sister, Andrew and Elizabteth, were raised by their parents, Chesley and Cheryl. After graduating from high school, he attended Simon Fraser University where his interest in organic chemistry was sparked by Professor Peter Wilson and Professor Robert Britton. Piercy graduated from Simon Fraser University in 2007 and moved to St. Catharines, Ontario, Canada in 2009 to pursue graduate studies with Professor Tomas Hudlicky. He is currently completing his Masters of Science in Chemistry.